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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  JAN 27  Source of Registration (SR) information in REGISTRY updated
                  and searchable
 NEWS  4  JAN 27  A new search aid, the Company Name Thesaurus, available in
                  CA/CAplus
 NEWS  5  FEB 05  German (DE) application and patent publication number format
                  changes
 NEWS  6  MAR 03  MEDLINE and LMEDLINE reloaded
 NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 03  FRANCEPAT now available on STN
 NEWS  9  MAR 29  Pharmaceutical Substances (PS) now available on STN
 NEWS 10  MAR 29  WPIFV now available on STN
 NEWS 11  MAR 29  New monthly current-awareness alert (SDI) frequency in RAPRA
 NEWS 12  APR 26  PROMT: New display field available
 NEWS 13  APR 26  IFIPAT/IFIUDB/IFICDB: New super search and display field
                  available
 NEWS 14  APR 26  LITALERT now available on STN
 NEWS 15  APR 27  NLDB: New search and display fields available
 NEWS 16  May 10  PROUSDDR now available on STN
 NEWS 17  May 19  PROUSDDR: One FREE connect hour, per account, in both May
                  and June 2004
 NEWS 18  May 12  EXTEND option available in structure searching
 NEWS 19  May 12  Polymer links for the POLYLINK command completed in REGISTRY

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)
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FILE 'HOME' ENTERED AT 15:48:26 ON 14 MAY 2004

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=> FIL STNGUIDE
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 7, 2004 (20040507/UP).

=> FIL HOME
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	0.27

FILE 'HOME' ENTERED AT 15:48:36 ON 14 MAY 2004

=> file registry
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.48

FILE 'REGISTRY' ENTERED AT 15:48:44 ON 14 MAY 2004
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STRUCTURE FILE UPDATES: 13 MAY 2004 HIGHEST RN 681515-11-7
DICTIONARY FILE UPDATES: 13 MAY 2004 HIGHEST RN 681515-11-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

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information enter HELP PROP at an arrow prompt in the file or refer
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http://www.cas.org/ONLINE/DBSS/registryss.html

=>
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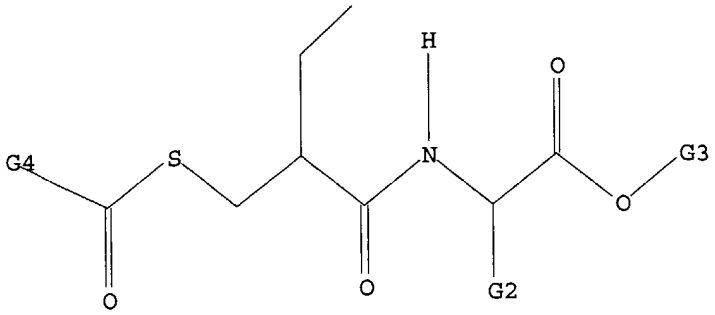
L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR

09986629



G1 C,Ph

G2 H,Ak

G3 H,Cy,Ak,Ph,o-C6H4,m-C6H4,p-C6H4

G4 Ph,o-C6H4,m-C6H4,p-C6H4,Cy,Ak

Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
FULL SEARCH INITIATED 15:49:17 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 2449 TO ITERATE

100.0% PROCESSED 2449 ITERATIONS 569 ANSWERS
SEARCH TIME: 00.00.01

L2 569 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.84	156.32

FILE 'CAPLUS' ENTERED AT 15:50:08 ON 14 MAY 2004
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FILE COVERS 1907 - 14 May 2004 VOL 140 ISS 21
FILE LAST UPDATED: 13 May 2004 (20040513/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2
L3 159 L2

09986629

=> d l3 bib abs

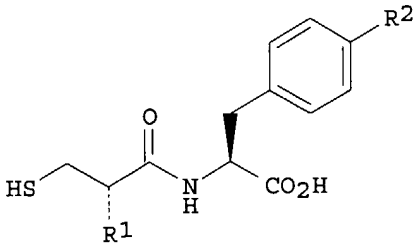
L3 ANSWER 1 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:991483 CAPLUS
DN 140:28047
TI Preparation of N-(mercaptoacyl)phenylalanine derivatives as inhibitors of angiotensin converting enzyme (ACE) and/or neutral endopeptidase (NEP)
IN Cooper, Anthony William James; Mordaunt, Jacqueline Elizabeth; Peace, Simon; Smith, Paul William; Smith, Steven
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003104200	A1	20031218	WO 2003-GB2446	20030605

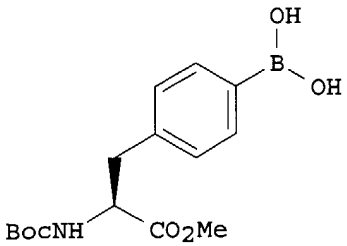
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	GB 2002-13119	A	20020607
	GB 2002-16856	A	20020719
	GB 2002-20875	A	20020909
	GB 2003-2543	A	20030204

OS MARPAT 140:28047
GI



I



II

AB Title compds. I (R1 = C1-6 alkyl; R2 = pyrazolyl, pyrimidinyl) or pharmaceutically acceptable derivs. were prepared for uses in medicine, particularly in the amelioration of a clin. condition for which an ACE and/or NEP inhibitor is indicated. For example, I (R1 = CHMe2, R2 = pyrimidin-5-yl) was prepared from the amidation of (S)-2-(acetylthio)methyl-3-methylbutanoic acid with Me 4-(5-pyrimidinyl)-L-phenylalaninate·HCl (obtained in two steps from phenylalanylboronate II and 5-bromopyrimidine), followed by saponification with NaOH. For inhibition activity, pKi of I (R1 = CHMe2, R2 = pyrimidin-5-yl) measured 8.1 against human kidney ACE, 6.9 against human plasma ACE, 6.1 against rat plasma ACE, and >8.5 against rabbit NEP.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s 2-159 bib abs l3
MISSING OPERATOR ABS L3
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d 2-159 bib abs l3

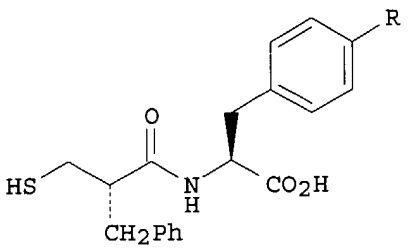
L3 ANSWER 2 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:991476 CAPLUS
DN 140:28046
TI Preparations of pyrazolyl-substituted N-(2-benzyl-3-mercaptopropionyl)phenylalanines as angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) inhibitors
IN Cooper, Anthony William James; Mordaunt, Jacqueline Elizabeth; Peace, Simon; Smith, Paul William; Smith, Steven
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003104189	A2	20031218	WO 2003-GB2502	20030605

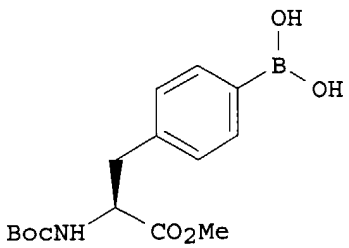
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2002-13122 A 20020607
OS MARPAT 140:28046
GI



I



II

AB Title compds. I (R = 1H-pyrazol-1-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl) or pharmaceutically acceptable derivs. were prepared for uses in medicine, particularly in the amelioration of a clin. condition for which an ACE and/or NEP inhibitor is indicated. For example, I (R = 1H-pyrazol-1-yl) was prepared from the amidation of (2S)-2-(acetylthio)methyl-3-phenylpropanoic acid by Me 4-(1H-pyrazol-1-yl)-L-phenylalaninate·HCl (obtained in two steps from

L-phenylalanylboronate II and 1H-pyrazole), followed by saponification with NaOH.
For inhibition activity: pKi of I (R = 1H-pyrazol-1-yl) measured 8.8 against human kidney ACE, <6.0 against human plasma ACE, 6.9 against rat plasma ACE, and >8.5 against rabbit NEP.

L3 ANSWER 3 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:950839 CAPLUS
DN 140:696
TI Combination of a DPP IV inhibitor and a cardiovascular compound
IN Holmes, David Grenville; Shetty, Suraj Shivappa; Hughes, Thomas Edward
PA Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003099279	A1	20031204	WO 2003-EP5639	20030528

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

PRAI GB 2002-12412 A 20020529
AB The invention relates to a combination therapy, such as a combined preparation or pharmaceutical composition, resp., comprising of a DPP IV inhibitor or a pharmaceutically acceptable salt thereof and a cardiovascular compound (being different from a statin) or a pharmaceutically acceptable salt thereof. The invention furthermore relates to the use of such a combination for the prevention, delay of progression or treatment of diseases and disorders selected from the group consisting of hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetes, especially type 2 diabetes mellitus, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:872198 CAPLUS
DN 140:146489
TI Process for the synthesis of enkephalinase inhibitor acetorphan
AU Zhou, Sheng-feng; Cheng, Guo-hou; Yang, Kai; Jiang, Wei-feng; Lin, Sheng-ping
CS College of Chemistry and Pharmaceutics, ECUST, Shanghai, 200237, Peop. Rep. China
SO Huadong Ligong Daxue Xuebao (2003), 29(4), 420-421
CODEN: HLIXEV; ISSN: 1006-3080
PB Huadong Ligong Daxue Xuebao Bianjibu

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DT Journal
LA Chinese
OS CASREACT 140:146489
AB Acetorphan. an oral enkephalinase inhibitor used in the treatment of acute diarrhea, was synthesized from benzyl chloride and di-Et malonate via alkylation, hydrolysis, Mannich reaction, decarboxylation and Michael addn, giving the intermediate 2-acetylthiomethyl-3-Ph propionic acid, further reacted with glycine benzyl ester to give the desired product with overall yield 17.4%.

L3 ANSWER 5 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:839697 CAPLUS
DN 139:345666
TI Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial
AU Alam, N. H.; Ashraf, H.; Khan, W. A.; Karim, M. M.; Fuchs, G. J.
CS Clinical Sciences Division, International Centre for Diarrhoeal Disease Research, Centre for Health and Population Research, Dhaka, Bangladesh
SO Gut (2003), 52(10), 1419-1423
CODEN: GUTTAK; ISSN: 0017-5749
PB BMJ Publishing Group
DT Journal
LA English
AB Background: The enkephalins, endogenous opiate substances, act as neurotransmitters along the entire digestive tract where they elicit intestinal antisecretory activity without affecting intestinal transit time or motility. Racecadotril, through inhibition of enkephalinase, reinforces the physiol. activity of endogenous enkephalins and, therefore, shows intestinal antisecretory activity. Aim: We conducted the study to determine the role of racecadotril as an adjunct to the standard treatment of cholera in adults. Methods: The study was a double blind, randomized, placebo controlled clin. trial involving 110 adult male cholera patients who received either racecadotril or placebo in addition to standard cholera treatment. The major outcome measures (stool output, oral rehydration solution (ORS) intake, requirements for unscheduled i.v. fluid infusion, and duration of diarrhea) were compared between the groups. Results: Of 110 patients enrolled, 54 received racecadotril and 56 received placebo. Admission clin. characteristics were comparable between the groups. There was no significant difference in (mean (SD)) total stool output (racecadotril v placebo 315 (228) v 280 (156) g/kg), total ORS intake (390 (264) v 369 (240) ml/kg), or duration of diarrhea (35 (15) v 32 (13) hours) between the groups. Clin. success, defined as resolution of diarrhea within 72 h of initiation of study intervention, was similar in both groups (racecadotril v placebo 96% v 89%). The number of patients receiving unscheduled i.v. infusions was not significantly different between the groups (racecadotril v placebo 22% v 14%). No drug related adverse effect was noted. Conclusion: The study demonstrated that racecadotril therapy, although found to be safe, does not provide addnl. benefit in the treatment of severe cholera in adults.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:656728 CAPLUS
DN 139:180345
TI Process for the preparation of 4-substituted phenylalanine ester derivs.
IN Cooke, Jason William Beames; Hayes, Douglas; Henson, Richard Anthony; Hermitage, Stephen Andrew; Ward, Richard Anthony; Whitehead, Andrew Jonathan
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2

09986629

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003068725	A2	20030821	WO 2003-EP1607	20030214
	WO 2003068725	A3	20031224		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2002-3665 A 20020215
OS CASREACT 139:180345; MARPAT 139:180345
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process for preparing 4-substituted phenylalanine ester derivs. I (R1 is H, alkyl or benzyl; R2 is H or a protecting group CHO or COC1-4alkyl; R3 is a 5- or 6-membered aromatic heterocycle with one or two heteroatoms selected from nitrogen, oxygen and sulfur) involves intermediates I (same R1 and R2, R3 is CN or NHNH3+). Compds. of this type are known to be useful in the preparation of compds. having mixed ACE-NEP inhibitor activity. Thus, phenylalanine derivative II was prepared via reaction of I (R1 = Me, R2 = CHO, R3 = CN) with NaSH/NH4Cl/DMAC and then BrCH2CH(OMe)2 to form the thiazole ring.

L3 ANSWER 7 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:459731 CAPLUS
DN 139:122572
TI Molecular Descriptors Influencing Melting Point and Their Role in Classification of Solid Drugs
AU Bergstroem, Christel A. S.; Norinder, Ulf; Luthman, Kristina; Artursson, Per
CS Center of Pharmaceutical Informatics, Department of Pharmacy, Uppsala University, Uppsala, SE-751 23, Swed.
SO Journal of Chemical Information and Computer Sciences (2003), 43(4), 1177-1185
CODEN: JCISD8; ISSN: 0095-2338
PB American Chemical Society
DT Journal
LA English
AB The aim of the study was to investigate whether easily and rapidly calculated 2D and 3D mol. descriptors could predict the m.p. of drug-like compds., to allow a m.p. classification of solid drugs. The m.ps. for 277 structurally diverse model drugs were extracted from the 12th edition of the Merck Index. 2D descriptors mainly representing electrotopol. and electron accessibilities were calculated by Molconn-Z and the AstraZeneca inhouse program Selma. 3D descriptors for mol. surface areas were generated using the programs MacroModel and Marea. Correlations between the calculated descriptors and the m.p. values were established with partial least squares projection to latent structures (PLS) using training and test

sets. Three different descriptor matrixes were studied, and the models obtained were used for consensus modeling. The calculated properties were shown to explain 63% of the m.p. Descriptors for hydrophilicity, polarity, partial atom charge, and mol. rigidity were found to be pos. correlated with m.p., whereas nonpolar atoms and high flexibility within the mol. were neg. correlated to this solid-state characteristic. Moreover, the studied descriptors were successful in providing a qual. ranking of compds. into classes displaying a low, intermediate, or high m.p. Finally, a mechanism for the relation between the mol. descriptors and their effect on the m.p. and the aqueous solubility was proposed.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:334829 CAPLUS
DN 138:343889
TI Novel pharmaceutical compounds containing drugs bound to polypeptides
IN Picariello, Thomas
PA New River Pharmaceuticals Inc., USA
SO PCT Int. Appl., 4662 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003034980	A2	20030501	WO 2001-US43089	20011114
	WO 2003034980	C1	20031120		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1401374	A1	20040331	EP 2001-274606	20011114
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2000-274622P	P	20001114		
	WO 2001-US43089	W	20011114		

AB Compns. comprising polypeptides and drugs covalently attached to the polypeptide are disclosed. Also provided is a method for delivery of these drugs to a patient comprising administering to the patient a composition comprising a polypeptide and a drug covalently attached to the polypeptide. Also provided is a method for protecting drugs from degradation comprising covalently attaching them to a polypeptide. Also provided is a method for controlling release of drugs from a composition comprising covalently attaching them to the polypeptide.

L3 ANSWER 9 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:234150 CAPLUS
DN 139:332690
TI Cardiovascular hypertrophy in diabetic spontaneously hypertensive rats: optimizing blockade of the renin-angiotensin system
AU Lassila, Markus; Davis, Belinda J.; Allen, Terri J.; Burrell, Louise M.; Cooper, Mark E.; Cao, Zemin
CS Baker Heart Research Institute, Melbourne, 8008, Australia
SO Clinical Science (2003), 104(4), 341-347
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.

09986629

DT Journal
LA English
AB The aim of the present study was to compare the antihypertrophic effects of blockade of the renin-angiotensin system (RAS), vasopeptidase inhibition and calcium channel antagonism on cardiac and vascular hypertrophy in diabetic spontaneously hypertensive rats (SHR). SHR with streptozotocin-induced diabetes were treated with one of the following therapies for 32 wk: the angiotensin-converting enzyme (ACE) inhibitor captopril (100 mg/kg); the angiotensin AT1 receptor antagonist valsartan (30 mg/kg); a combination of captopril with valsartan; the vasopeptidase inhibitor mixanpril (100 mg/kg); or the calcium channel antagonist amlodipine (6 mg/kg). Systolic blood pressure and cardiac and mesenteric artery hypertrophy were assessed. Mean systolic blood pressure in diabetic SHR (200±5 mmHg) was reduced by captopril (162±5 mmHg), valsartan (173±5 mmHg), mixanpril (176±2 mmHg) and amlodipine (159±4mmHg), and was further reduced by the combination of captopril with valsartan (131±5mmHg). Captopril, valsartan and mixanpril reduced heart and left ventricle wts. by approx. 10%. The combination of captopril and valsartan further reduced heart weight (-24%) and left ventricular weight (-29%). Amlodipine did not affect cardiac hypertrophy. Only mixanpril and the combination of captopril and valsartan significantly reduced mesenteric weight The mesenteric wall/lm ratio was reduced by all drugs, and to a greater extent by the combination of captopril and valsartan. We conclude that optimizing the blockade of vasoconstrictive pathways such as the RAS, particularly with the combination of ACE inhibition and AT1 receptor antagonism, is associated with antitrophic effects in the context of diabetes and hypertension. In contrast, calcium channel blockade, despite similar effects on blood pressure, confers less antitrophic effects in the diabetic heart and blood vessels.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:59010 CAPLUS
DN 139:30527
TI Effects of Dual Angiotensin-Converting Enzyme and Neutral Endopeptidase 24-11 Chronic Inhibition by Mixanpril on Insulin Sensitivity in Lean and Obese Zucker Rats
AU Arbin, Valerie; Claperon, Nicole; Fournie-Zaluski, Marie-Claude; Roques, Bernard P.; Peyroux, Jacques
CS Laboratoire de Pharmacologie, Faculte des Sciences Pharmaceutiques et Biologiques, Paris, Fr.
SO Journal of Cardiovascular Pharmacology (2003), 41(2), 254-264
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The aim of this study was to examine the effects of chronic (8-day) oral treatment with the dual angiotensin-converting enzyme (ACE) and neutral endopeptidase 24-11 (NEP) inhibitor mixanpril (25 mg/kg twice a day), compared with the ACE inhibitor captopril (25 mg/kg twice a day), on whole body insulin-mediated glucose disposal in young (10-wk) and old (19-wk) obese Zucker rats (ZOs). Moreover, the effects of chronic mixanpril administration on femoral blood flow at rest and during an insulin infusion were assessed. In the young ZOs, mixanpril decreased the glucose response during an IV glucose tolerance test more effectively than did captopril (-49 and -30%, resp., $p < 0.05$). Incremental glucose area under the curve in mixanpril-treated ZOs was then no longer different from that observed in vehicle-treated lean rats (1,592±175 and 1, 470±104 mg/dL + min, resp.). The beneficial effects resulting from mixanpril or captopril administration were observed in ZOs but not in lean littermates.

In the old ZOs, mixanpril induced higher glucose infusion rates to maintain euglycemia than did captopril during a hyperinsulinemic euglycemic clamp test (+92 and +35%, resp., $p < 0.001$). However, the glucose infusion rates in mixanpril-treated ZOs remained much lower than that observed in vehicle-treated lean rats (9.4±0.7 mg/kg/min vs. 28.6±1.0 mg/kg/min, $p < 0.001$). Mixanpril did not affect resting femoral vascular bed hemodynamics but restored the femoral blood flow response to insulin infusion. In conclusion, in ZOs, chronic dual ACE/NEP inhibition improves whole body insulin-mediated glucose disposal more effectively than does ACE inhibition alone. This beneficial effect seems to be restricted to conditions of insulin resistance and not directly linked to the improvement in the femoral blood flow response to insulin.

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:978628 CAPLUS
DN 138:49938
TI Nucleic acids for the prevention and treatment of gastric ulcers
IN Bratzler, Robert L.; Petersen, Deanna M.
PA USA
SO U.S. Pat. Appl. Publ., 45 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002198165	A1	20021226	US 2001-920313	20010801
PRAI US 2000-222248P	P	20000801		

OS MARPAT 138:49938
AB The invention relates to methods and products for treating gastric ulcers. A nucleic acid and optionally an anti-ulcer agent are administered to a subject to prevent or treat gastric ulcer.

L3 ANSWER 12 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:796294 CAPLUS
DN 139:127655
TI Effects of Chronic Neutral Endopeptidase Inhibition on the Progression of Left Ventricular Dysfunction and Remodeling in Dogs with Moderate Heart Failure
AU Mishima, Takayuki; Tanimura, Mitsuhiro; Suzuki, George; Todor, Anastassia; Sharov, Victor G.; Tanhehco, Elaine J.; Goldstein, Sidney; Sabbah, Hani N.
CS Division of Cardiovascular Medicine, Department of Medicine, Henry Ford Heart and Vascular Institute, Detroit, MI, USA
SO Cardiovascular Drugs and Therapy (2002), 16(3), 209-214
CODEN: CDTHET; ISSN: 0920-3206
PB Kluwer Academic Publishers
DT Journal
LA English
AB Background. The diuretic actions of endogenously produced atrial natriuretic factor (ANF) may be beneficial in the treatment of chronic heart failure (CHF). Neutral endopeptidase (NEP) is the primary enzyme responsible for the degradation of ANF. The present study investigates the effects of long-term NEP inhibition on the progression of left ventricular (LV) dysfunction and remodeling in dogs with moderate heart failure. Methods. LV dysfunction was produced in 12 dogs by multiple sequential intracoronary microembolizations. Embolizations were discontinued when LV ejection fraction (EF) was between 30-40%. Two weeks after the last embolization, dogs were randomized to 3 mo of oral therapy with the NEP inhibitor ecadotril (100 mg, once daily, n = 6) or to no therapy at all (control, n = 6). Results. During the 3 mo of follow-up, LV EF in

control dogs decreased from 37±1% to 28±1% (P < 0.01) and LV end-diastolic volume (EDV) and end-systolic volume (ESV) increased (EDV: 72±3 vs. 84±5 mL, P < 0.01); (ESV: 45±1 vs. 60±4 mL, P < 0.01). In dogs treated with ecadotril, LV EF (34±1% vs. 37±2%), EDV (79± 5 vs. 78±6 mL) and ESV (52±3 vs. 49±4) remained essentially unchanged after 3 mo of therapy. Histomorphometric measurements at the termination of the study showed that ecadotril was associated with significantly reduced cardiomyocyte hypertrophy compared to control. Conclusion. Early, long-term NEP inhibition with ecadotril prevents the progression of LV dysfunction and attenuates progressive LV remodeling in dogs with moderate heart failure.

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:596667 CAPLUS
DN 137:273031
TI A multinational comparison of racecadotril and loperamide in the treatment of acute watery diarrhoea in adults
AU Prado, D.
CS Global Adult Racecadotril Study Group, Hospital Centro Medico, Guatemala, Guatemala
SO Scandinavian Journal of Gastroenterology (2002), 37(6), 656-661
CODEN: SJGRA4; ISSN: 0036-5521
PB Taylor & Francis
DT Journal
LA English
AB Racecadotril (acetorphan) is an orally active, potent inhibitor of enkephalinase, which exerts an antihypersecretory effect without increasing intestinal transit time. The aim of this study was to compare the efficacy, safety and tolerability of racecadotril with those of loperamide by assessing their effects on the resolution of the signs and symptoms of diarrhea in patients in developing countries who had acute watery diarrhea of less than 5 days' duration. 945 Outpatients from 21 centers in 14 countries received racecadotril (100 mg) or loperamide (2 mg) three times daily in a single-blind study. Duration of diarrhea was the primary measure of efficacy; secondary criteria were overall clin. response, occurrence and duration of abdominal pain and distension, and occurrence of other associated signs and symptoms. Occurrence of constipation and adverse events were the main safety assessments. Diarrhea resolved rapidly with both racecadotril and loperamide (55.0 h in both groups), 92% of patients on racecadotril and 93% on loperamide being treatment successes. Racecadotril produced a significantly greater reduction in abdominal pain and distension than loperamide (P=0.024 and 0.03, resp.). The duration of abdominal distension was significantly shorter with racecadotril (5.4 vs. 24.4 h; P=0.0001), and constipation was also significantly less frequent (16% vs. 25%; P=0.001). One-hundred-and-eighty patients (19%) experienced one or more adverse event during the study: 67 (14.2%) in the racecadotril group and 113 (23.9%) in the loperamide group (P=0.001). Racecadotril resolved the symptoms of acute diarrhea rapidly and effectively, and produced more rapid resolution of abdominal symptoms and less constipation than loperamide.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

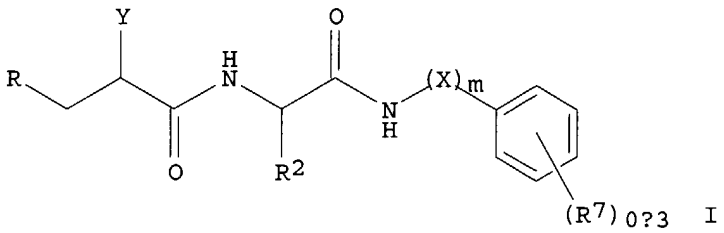
L3 ANSWER 14 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:594810 CAPLUS
DN 137:155177
TI Preparation and ophthalmic compositions of amino acid amides for treating ocular hypertension
IN Garcia, Maria L.; Kaczorowski, Gregory J.; Gao, Ying-Duo
PA Merck & Co., Inc., USA

09986629

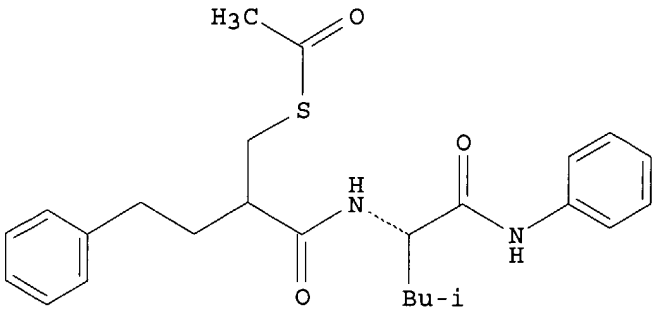
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002060863	A1	20020808	WO 2002-US3049	20020124
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1358153	A1	20031105	EP 2002-720887	20020125
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2004054213	A1	20040318	US 2003-466878	20030716
PRAI	US 2001-264954P	P	20010130		
	WO 2002-US3049	W	20020124		

OS MARPAT 137:155177
GI



I



II

AB The compds. with a general formula of I [wherein R and R2 = independently alkyl, (CH2)n(hetero)aryl, (CH2)nheterocycloalkyl, said alkyl or (hetero)aryl optionally substituted with 1-3 groups of R3; Y = (CH2)nSCOR4; X = CH2 or O in which m = 1; R3 = H, alkoxy, alkyl(amino), CF3, NO2, NH2, CN, or halo; R4 = alkoxy or alkyl; R7 = H, halo, OH, NO2, NH2, CN, alkoxycarbonyl, CO2H, haloalkyl, alkoxycarbonylalkyl, or alkylsulfonyl; m = 1-3; n = 0-3; or a pharmaceutically acceptable salt, enantiomer, diastereomer, or mixture thereof] were prepared For example, L-leucine derivative II was prepared in a 7-step synthesis involving condensation of 4-phenyl-2-(acetylthiomethyl)butyric acid and (S)-leucine t-Bu ester and amidation with aniline (50%). This invention relates to

the use of potent potassium channel blockers or formulations thereof in the treatment of glaucoma and other conditions which leads to elevated intraoccular pressure in the eye of a patient. This invention also relates to the use of such compds. to provide a neuroprotective effect to the eye of mammalian species, particularly humans. The compds. I were found to cause concentration dependent inhibition of the fluorescence ratio with IC50 values in the range of 10 nM to 5 μM, more preferably from 100 nM to 1 μM.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:556104 CAPLUS
DN 137:109489
TI Compositions comprising a polypeptide and an active agent
IN Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal J.
PA USA
SO U.S. Pat. Appl. Publ., 34 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 11

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002099013	A1	20020725	US 2001-933708	20010822
	US 2004087483	A1	20040506	US 2002-136433	20020502
PRAI	US 2000-247556P	P	20001114		
	US 2000-247558P	P	20001114		
	US 2000-247559P	P	20001114		
	US 2000-247560P	P	20001114		
	US 2000-247561P	P	20001114		
	US 2000-247594P	P	20001114		
	US 2000-247595P	P	20001114		
	US 2000-247606P	P	20001114		
	US 2000-247607P	P	20001114		
	US 2000-247608P	P	20001114		
	US 2000-247609P	P	20001114		
	US 2000-247610P	P	20001114		
	US 2000-247611P	P	20001114		
	US 2000-247612P	P	20001114		
	US 2000-247620P	P	20001114		
	US 2000-247621P	P	20001114		
	US 2000-247634P	P	20001114		
	US 2000-247635P	P	20001114		
	US 2000-247698P	P	20001114		
	US 2000-247699P	P	20001114		
	US 2000-247700P	P	20001114		
	US 2000-247701P	P	20001114		
	US 2000-247702P	P	20001114		
	US 2000-247797P	P	20001114		
	US 2000-247798P	P	20001114		
	US 2000-247799P	P	20001114		
	US 2000-247800P	P	20001114		
	US 2000-247801P	P	20001114		
	US 2000-247802P	P	20001114		
	US 2000-247803P	P	20001114		
	US 2000-247804P	P	20001114		
	US 2000-247805P	P	20001114		
	US 2000-247807P	P	20001114		
	US 2000-247832P	P	20001114		
	US 2000-247833P	P	20001114		

	US 2000-247926P	P	20001114
	US 2000-247927P	P	20001114
	US 2000-247928P	P	20001114
	US 2000-247929P	P	20001114
	US 2000-247930P	P	20001114
	US 2000-642820	A2	20000822
	US 2000-248607P	P	20001116
	US 2001-933708	A2	20010822

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

L3 ANSWER 16 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:394515 CAPLUS
DN 137:185774
TI Strategies for access to enantiomerically pure ecadotril, dexecadotril and fasidotril: a review
AU Monteil, Thierry; Danvy, Denis; Sihel, Miryam; Leroux, Richard; Plaquevent, Jean-Christophe
CS Faculte des Sciences, Universite de Rouen, Mont-Saint-Aignan, F-76821, Fr.
SO Mini-Reviews in Medicinal Chemistry (2002), 2(3), 209-217
CODEN: MMCIAE; ISSN: 1389-5575
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Ecadotril and dexecadotril are powerful and selective inhibitors of neprilysin (NEP, EC 3.4.24.11) and are being developed as therapeutic agents, since they behave as prodrugs of the enantiomers of thiorphan. They exhibit different pharmaceutical profiles (intestinal antisecretatory action for the (R) enantiomer, i.e. dexecadotril, and cardiovascular activity for the (S) enantiomer, i.e. ecadotril). Fasidotril is a related compound which has special interest as an equipotent dual inhibitor of NEP and ACE (EC 3.4.15.1). This behavior confers on fasidotril powerful pharmaceutical properties in the cardiovascular field. This review deals with various synthetic approaches, either published or patented, for access to the enantiomerically pure or highly enriched forms of these drugs. Thus, different methods have been studied, which are taken from different methodologies of resolution procedures and asym. synthesis, namely:. I- Synthesis from a chiron from the chiral pool. Ii- Chemical resolution of racemic precursors. Iii- Enzymic resolution and desymmetrization of meso starting materials. Iv- Asym. synthesis, including enantioselective catalytic hydrogenation, alkaloid catalyzed asym. Michael addns., and diastereoselective alkylation of a chiral derivative Some of these methods are used in industrial processes leading to the indicated compds.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:391512 CAPLUS
DN 136:402027
TI Preparation of amino acid derivatives for modulating angiotensin converting enzyme-2 (ACE-2)
IN Acton, Susan L.; Ocain, Timothy D.; Gould, Alexandra E.; Dales, Natalie A.; Guan, Bing; Brown, James A.; Patane, Michael; Kadambi, Vivek J.; Solomon, Michael; Stricker-Krongrad, Alain
PA Millennium Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 395 pp.

09986629

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002039997	A2	20020523	WO 2001-US45703	20011031
	WO 2002039997	A3	20021128		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	AU 2002039454	A5	20020527	AU 2002-39454	20011031
PRAI	US 2000-704216	A	20001101		
	US 2001-870382	A	20010529		
	US 2001-371741P	P	20011019		
	WO 2001-US45703	W	20011031		

OS MARPAT 136:402027

AB ACE-2 modulating compds. Z-A-B-E (Z is a zinc coordinating moiety; E is an enzyme coordinating moiety; A is an auxiliary pocket binding moiety; B is a side chain binding moiety) were prepared for the treatment of body weight disorders. Thus, N-[(S)- or (R)-1-carboxy-3-phenylpropyl]-L-leucine was prepared by the solid-phase method and showed ACE-2 inhibitory activity.

L3 ANSWER 18 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:354100 CAPLUS
DN 136:355480
TI Process for the synthesis of N-(mercaptoacyl) amino acid derivatives from α-substituted acrylic acids
IN Monteil, Thierry; Danvy, Denis; Plaquevent, Jean-christophe; Duhamel, Pierre; Duhamel, Lucette; Lecomte, Jeanne-marie; Schwartz, Jean-charles; Piettre, Serge
PA Fr.
SO U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002055645	A1	20020509	US 2001-986629	20011109
	FR 2816309	A1	20020510	FR 2000-14419	20001109
	FR 2816309	B1	20021227		
	EP 1205476	A1	20020515	EP 2001-402833	20011031
	EP 1205476	B1	20030423		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

	AT 238292	E	20030515	AT 2001-402833	20011031
	ES 2198389	T3	20040201	ES 2001-1402833	20011031
	JP 2002234869	A2	20020823	JP 2001-341890	20011107
PRAI	FR 2000-14419	A	20001109		

OS CASREACT 136:355480; ~~MARPAT 136:355480~~

AB Amino acid derivs. R4SCH2CH(CH2R1)CONHCHR2CO2R3 [I; R1 = Ph or 3,4-methylenedioxyphenyl; R2 = H or alkyl; R3 = H, alkyl, or phenylalkyl; R4 = aliphatic or aromatic acyl] were prepared via Michael addition of a thioacid R4SH to an α-substituted acrylamide derivative The invention also

relates to the enantioselective synthesis of compds. I where R2 is other than H, in the preferential (S,S) configuration:. Thus, benzyl N-(S)-[2-[(acetylthio)methyl]-1-oxo-3-(3,4-methylenedioxyphenyl)propyl]-(S)-alaninate (fasidotril) was prepared in 30% overall yield by conversion of piperonylacrylic acid to the acid chloride, coupling with benzyl (methylsulfonyl)-L-alaninate, and Michael addition reaction with thioacetic acid.

L3 ANSWER 19 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:332011 CAPLUS
DN 136:355482
TI Compositions comprising a polypeptide and an active agent
IN Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J.
PA New River Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 11

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002034237	A1	20020502	WO 2001-US26142	20010822
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 6716452	B1	20040406	US 2000-642820	20000822
	AU 2001086599	A5	20020506	AU 2001-86599	20010822
	EP 1311242	A1	20030521	EP 2001-966056	20010822
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2000-642820	A	20000822		
	WO 2001-US26142	W	20010822		

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:935400 CAPLUS
DN 136:58842
TI Pharmaceutical preparations comprising racecadotril (acetorphan)
IN Barges Causeret, Nathalie Claude Marianne; Giraud, Jean-Philippe
PA Laboratoire Glaxosmithkline, Fr.
SO PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001097803	A1	20011227	WO 2001-EP7007	20010620

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2000-15490 A 20000623

AB A new pharmaceutical granulate formulation comprising the antidiarrheal agent racecadotril comprising at least one diluent, at least one lubricant, and an intragranular disintegrant having defined characteristics. For example, granules were prepared containing racecadotril 100 mg, Mg stearate 4 mg, Aerosil R972 2 mg, lactose 41 mg, and gelatinized maize starch (Amidon C Pharm 93000) 78 mg. The granules were calibrated on a 1.25 mm sieve and filled into capsules.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:935398 CAPLUS
DN 136:58841
TI Dry powder granulated formulation of racecadotril for use as an antidiarrheal
IN Lecomte, Jeanne-Marie; Schwartz, Jean-Charles
PA Societe Civile Bioprojet, Fr.
SO PCT Int. Appl., 7 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001097801	A2	20011227	WO 2001-EP7086	20010622
	WO 2001097801	A3	20020912		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1294372	A2	20030326	EP 2001-969310	20010622
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2003166718	A1	20030904	US 2003-347332	20030113
	BG 107481	A	20030930	BG 2003-107481	20030120
PRAI	EP 2000-401799	A	20000623		
	WO 2001-EP7086	W	20010622		

AB A dry powder granulated formulation of racecadotril and its use in therapy in the treatment of diarrhea. A dry powder was prepared from sucrose 96.65, Eudragit NE30D 0.15, apricot flavor 2.00, colloidal silica 0.20, and racecadotril 1.00%.

L3 ANSWER 22 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:931966 CAPLUS
DN 137:118821
TI Neutral Peptidase Inhibitors
AU Ray, Indranill Basu; Reddy, Kathi Narasimha

09986629

CS Division of Interventional Cardiology, Vijaya Heart Foundation, Chennai, India
SO HeartDrug (2001), 1(4), 236-240
CODEN: HEARCO; ISSN: 1422-9528
PB S. Karger AG
DT Journal; General Review
LA English
AB A review. End-stage heart disease has a high mortality. Despite considerable advancement in therapy, the overall prognosis remains dismal. This has spurred the search for newer agents that can effectively attenuate the aberrant physiol. changes evident in heart failure. Multiple clin. trials have made it evident that opposing the aberrant neurohormonal stimulation is associated with a better outcome. Thus ACE inhibitors which reduce afterload by reducing the formation of angiotensin II have a better effect on mortality and morbidity than hydralazine, a direct vasodilator. Similarly, certain studies albeit small ones have shown that natriuretic agents which promote diuresis by augmenting the body's defense against the abnormal neurohormonal milieu evident in heart failure might have a better effect on long-term prognosis than the symptomatically much more effective diuretics. These findings have led to the development of novel agents that not only block the overstimulated renin-angiotensin system but also augment the natriuretic peptide system, the body's defense against the abnormal neurohormonal milieu that is evident in heart failure. This article reviews the clin. pharmacol. of novel agents that augment the natriuretic peptide system in the body.
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:836453 CAPLUS
DN 136:128808
TI The antiarrhythmic effect of enkephalinase inhibitors
AU Lishmanov, Yu. B.; Maslov, L. N.; Uskinha, E. V.
CS Laboratory of Experimental Cardiology, Institute of Cardiology, Tomsk Scientific Center, Siberian Division, Russian Academy of Medical Sciences, Tomsk, 634050, Russia
SO Eksperimental'naya i Klinicheskaya Farmakologiya (2001), 64(5), 28-30
CODEN: EKFAE9; ISSN: 0869-2092
PB Izdatel'stvo Folium
DT Journal
LA Russian
AB I.v. pretreatment with the enkephalinase inhibitors KB 101 and acetorphan increased heart resistance to the arrhythmogenic action of adrenaline (epinephrine) and is related to the activation of δ-opioid receptors by endogenous enkephalins. At the same time, the μ-receptors and their endogenous agonists play an insignificant role in the development of the antiarrhythmic effect of acetorphan. The enkephalinase inhibitors are a promising group of compds. for the development of new antiarrhythmic drugs, because these agents, in contrast to opiates, do not lead to narcotic addiction.

L3 ANSWER 24 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:490673 CAPLUS
DN 135:267013
TI Acute effect of the dual angiotensin-converting enzyme and neutral endopeptidase 24-11 inhibitor mixanpril on insulin sensitivity in obese Zucker rat
AU Arbin, V.; Claperon, N.; Fournie-Zaluski, M.-C.; Roques, B. P.; Peyroux, J.
CS Laboratoire de Pharmacologic, U266 INSERM, UMR 8600 CNRS, U.F.R. des Sciences Pharmaceutiques et Biologiques, Paris, 75 006, Fr.
SO British Journal of Pharmacology (2001), 133(4), 495-502

09986629

CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB The aim of this study was to determine whether acute dual angiotensin-converting enzyme (ACE)/neutral endopeptidase 24-11 (NEP) inhibition could improve whole body insulin-mediated glucose disposal (IMGD) more than ACE inhibition alone and whether this effect was mediated by the kinin-nitric oxide (NO) pathway activation. We therefore compared in anesthetized obese (fa/fa) Zucker rats (ZOs) the effects of captopril (2 mg kg-1, i.v. + 2 mg kg-1 h-1), retrothiorphan (25 mg kg-1, i.v. + 25 mg kg-1 h-1), a selective NEP inhibitor, and mixanpril (25 mg kg-1, i.v. + 25 mg kg-1 h-1), a dual ACE/NEP inhibitor, on IMGD using hyperinsulinemic euglycemic clamp technique. The role of the kinin-NO pathway in the effects of mixanpril was tested using a bradykinin B2 receptor antagonist (Hoe-140, 300 μg kg-1) and a NO-synthase inhibitor (Nω-nitro-L-arginine Me ester, L-NAME, 10 mg kg-1 i.v. + 10 mg kg-1 h-1) as pretreatments. Insulin sensitivity index (ISI) was lower in ZO controls than in lean littermates. Increases in ISI were observed in captopril- and retrothiorphan-treated ZOs. In mixanpril-treated ZOs, ISI was further increased, compared to captopril- and retrothiorphan-treated ZOs. In ZOs, Hoe-140 and L-NAME alone did not significantly alter and slightly reduced the ISI resp. Hoe-140 and L-NAME markedly inhibited the ISI improvement induced by mixanpril. These results show that in obese insulin-resistant Zucker rats, under acute conditions, NEP or ACE inhibition can improve IMGD and that dual ACE/NEP inhibition improves IMGD more effectively than does either single inhibition. This effect is linked to an increased activation of the kinin-NO pathway.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:461240 CAPLUS
DN 135:262362
TI Determination of racecadotril by HPLC
AU Zhao, Zhe; Liu, Shuchun
CS Tianjin Municipal Institute for Drug Control, Tianjin, 300070, Peop. Rep. China
SO Zhongguo Yaoxue Zazhi (Beijing, China) (2001), 36(4), 267-269
CODEN: ZYZAEU; ISSN: 1001-2494
PB Zhongguo Yaoxue Zazhishe
DT Journal
LA Chinese
AB The purity of racecadotril and content of impurity benzylthiorphan disulfide were determined by HPLC at 210 nm on ODS column with acetonitrile-KH2PO4 buffer (70:30) as mobile phase. The linear range for racecadotril was 0.08-0.24 mg mL-1 and that of benzylthiorphan disulfide was 2.40-21.56 μg mL-1 (r = 0.999 9). The detection limit was 1 μg mL-1. The average recovery was 100.0% with RSD of 0.78% (n = 6). The results showed that the method was convenient, accurate, and specific.

L3 ANSWER 26 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:233851 CAPLUS
DN 135:190150
TI Efficacy and tolerability of racecadotril in acute diarrhea in children
AU Cezard, Jean Pierre; Duhamel, Jean Francois; Meyer, Martine; Pharaon, Isabelle; Bellaiche, Marc; Maurage, Chantal; Ginies, Jean Louis; Vaillant, Jean Michel; Girardet, Jean Philippe; Lamireau, Thierry; Poujol, Alain; Morali, Alain; Sarles, Jacques; Olives, Jean Pierre; Whately-Smith, Caroline; Audrain, Sylvie; Lecomte, Jeanne Marie
CS Pediatric Gastroenterology Unit, Paris, Fr.
SO Gastroenterology (2001), 120(4), 799-805

09986629

CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Oral rehydration therapy is the only treatment recommended by the World Health Organization in acute diarrhea in children. Antisecretory drugs available could not be used because of their side effects, except for racecadotril, which is efficient in acute diarrhea in adults. The efficacy and tolerability of racecadotril (1.5 mg/kg administered orally 3 times daily) as adjuvant therapy to oral rehydration were compared with those of placebo in 172 infants aged 3 mo to 4 yr (mean age, 12.8 mo) who had acute diarrhea. The treatment groups were comparable in terms of age, duration of diarrhea, number of stools, and causative microorganism at inclusion. During the first 48 h of treatment, patients receiving racecadotril had a significantly lower stool output (grams per h) than those receiving placebo. The 95% confidence interval was 43%-88% for the full data set (n = 166; P = 0.009) and 33%-75% for the per-protocol population (n = 116; P = 0.001). There was no difference between treatments depending on rotavirus status. Significant differences between treatment groups were also found after 24 h of treatment: full data set (n = 167; P = 0.026) and per-protocol population (n = 121; P = 0.015). Tolerability was good in both groups of patients. This study demonstrates the efficacy (up to 50% reduction in stool output) and tolerability of racecadotril as adjuvant therapy to oral rehydration solution in the treatment of severe diarrhea in infants and children.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:184147 CAPLUS
DN 134:367157
TI New asymmetric synthesis of dexecadotril and ecadotril starting from a single precursor
AU Monteil, Thierry; Danvy, Denis; Plaquevent, Jean-Christophe; Duhamel, Lucette; Duhamel, Pierre; Gros, Claude; Schwartz, Jean-Charles; Lecomte, Jeanne-Marie
CS Bioprojet, Paris, F-75003, Fr.
SO Synthetic Communications (2001), 31(2), 211-218
CODEN: SYNCAV; ISSN: 0039-7911
PB Marcel Dekker, Inc.
DT Journal
LA English
OS CASREACT 134:367157
AB A method providing access to both enantiomers of 3-acetylthio-2-benzylpropionic acid via enzymic desymmetrization of 2-benzyl-1,3-propanediol was developed. These compds. are resp. the starting materials for the synthesis of ecadotril, and dexecadotril, which are powerful inhibitors of NEP (EC 3.4.24.11) and have been developed as therapeutic agents.
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 28 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:167787 CAPLUS
DN 134:202715
TI Pharmaceutical formulations of ACE and ATII inhibitors for prevention of stroke, diabetes and/or congestive heart failure
IN Schoelkens, Bernward; Bender, Norbert; Rangoonwala, Badrudin; Dagenais, Gilles; Gerstein, Hertzel; Ljunggren, Anders; Yusuf, Salim
PA Aventis Pharma Deutschland G.m.b.H., Germany
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2

09986629

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001015673	A2	20010308	WO 2000-EP8341	20000825
	WO 2001015673	A3	20020307		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2000013540	A	20020430	BR 2000-13540	20000825
	EP 1212081	A2	20020612	EP 2000-965898	20000825
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	TR 200200518	T2	20020621	TR 2002-20020051820000825	
	TR 200202466	T2	20021223	TR 2002-20020246620000825	
	TR 200202467	T2	20021223	TR 2002-20020246720000825	
	JP 2003508426	T2	20030304	JP 2001-519887	20000825
	EE 200200085	A	20030415	EE 2002-85	20000825
	BG 106319	A	20021229	BG 2002-106319	20020118
	NO 2002000850	A	20020221	NO 2002-850	20020221
	ZA 2002001471	A	20030303	ZA 2002-1471	20020221
PRAI	SE 1999-3028	A	19990827		
	WO 2000-EP8341	W	20000825		

AB The present invention relates to use of an inhibitor of the renin-angiotensin system (RAS), i.e., inhibitors of angiotensin-converting enzyme (ACE) and angiotensin II type 1 receptor (ATII) antagonists or a pharmaceutically acceptable derivative thereof, particularly ramipril or ramiprilat, in the manufacture of a medicament for the prevention and/or treatment of stroke, diabetes and/or congestive heart failure (CHF). A large-scale clin. trial was designed to examine the effect of the ACE inhibitor ramipril vs. placebo in reducing cardiovascular events. There was a clear 32% reduction in the ramipril group in the number of patients who developed a stroke, and this is surprising since patients were normotensive when recruited to the study. The number of patients who developed CHF was significantly reduced by 21% in the ramipril group, which is unexpected since patients had no signs or symptoms of CHF at study start. Equally surprising is the marked 36% reduction in the number of patients who developed diabetes in the ramipril group.

L3 ANSWER 29 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:137173 CAPLUS
DN 134:178396
TI Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
IN Del Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001012584	A2	20010222	WO 2000-EP7225	20000727
	WO 2001012584	A3	20020829		

W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	BR 2000013264	A	20020416	BR 2000-13264	20000727
	EP 1252133	A2	20021030	EP 2000-953102	20000727
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003515526	T2	20030507	JP 2001-516885	20000727
	ZA 2002000628	A	20030423	ZA 2002-628	20020123
	NO 2002000623	A	20020409	NO 2002-623	20020208
PRAI	IT 1999-MI1817	A	19990812		
	WO 2000-EP7225	W	20000727		

OS MARPAT 134:178396

AB Compds. or their salts of general formula (I): A-B-N(O)s wherein: s is an integer equal to 1 or 2; A = R-T1-, wherein R is the drug radical and T1 = (CO)t or (X)t', wherein X = O, S, NR1c, R1c is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -TB -X2-O- wherein TB = (CO) when t = 0, TB = X when t' = 0, X being as above defined; X2, bivalent radical, is such that the precursor drug of A and the precursor of B meet resp. the pharmacol. tests described in the description. Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

L3 ANSWER 30 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:742057 CAPLUS
DN 133:309791
TI Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
IN Del Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 140 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000061541	A2	20001019	WO 2000-EP3239	20000411
	WO 2000061541	A3	20010927		
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	IT 1311923	B1	20020320	IT 1999-MI752	19990413
	BR 2000009703	A	20020108	BR 2000-9703	20000411
	EP 1169298	A2	20020109	EP 2000-926870	20000411
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002541236	T2	20021203	JP 2000-610818	20000411
	TR 200102928	T2	20021223	TR 2001-20010292	20000411
	NZ 514270	A	20040227	NZ 2000-514270	20000411
	ZA 2001008126	A	20030403	ZA 2001-8126	20011003

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	NO 2001004928	A	20011213	NO 2001-4928	20011010
PRAI	IT 1999-MI752	A	19990413		
	WO 2000-EP3239	W	20000411		

OS MARPAT 133:309791

AB Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

L3 ANSWER 31 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:742053 CAPLUS

DN 133:310142

TI Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction

IN Del Soldato, Piero

PA Nicox S.A., Fr.

SO PCT Int. Appl., 159 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000061537	A2	20001019	WO 2000-EP3234	20000411
	WO 2000061537	A3	20010927		
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	IT 1311924	B1	20020320	IT 1999-MI753	19990413
	BR 2000009702	A	20020108	BR 2000-9702	20000411
	EP 1169294	A2	20020109	EP 2000-925203	20000411
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002541233	T2	20021203	JP 2000-610814	20000411
	ZA 2001008127	A	20030103	ZA 2001-8127	20011003
	NO 2001004927	A	20011213	NO 2001-4927	20011010
PRAI	IT 1999-MI753	A	19990413		
	WO 2000-EP3234	W	20000411		

OS MARPAT 133:310142

AB Compds. A-B-C-N(O)s and A-C1[N(O)s]-B1 or their salts [s is an integer 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacol. tests reported in the description; C and C1 are two bivalent radicals; the precursors of the radicals B and B1 are such as to meet the pharmacol. test reported in the description] were prepared for use as pharmaceuticals. Thus, (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalenylacetyl)cysteine 4-nitroxybutyl ester was prepared (NCX 2101) from naproxene and N-acetylcysteine in the first of 28 synthetic examples given. Pharmacol. test examples and tabular data are also given.

L3 ANSWER 32 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:630679 CAPLUS

DN 134:125777

TI Racecadotril in the treatment of acute watery diarrhea in children

AU Salazar-Lindo, Eduardo; Santisteban-Ponce, Javier; Chea-Woo, Elsa; Gutierrez, Manuel

CS Department of Pediatrics, Hospital Nacional Cayetano Heredia, Lima, Peru

SO New England Journal of Medicine (2000), 343(7), 463-467
CODEN: NEJMAG; ISSN: 0028-4793

09986629

PB Massachusetts Medical Society
DT Journal
LA English
AB Racecadotril (acetorphan), an enkephalinase inhibitor with antisecretory and antidiarrheal actions, is an effective and safe treatment for acute diarrhea in adults and children. Whether treatment with racecadotril and oral rehydration therapy is more effective than treatment with oral rehydration alone in hospitalized children with acute watery diarrhea is not known. We treated 135 boys 3 to 35 mo of age who had watery diarrhea of five days' duration or less with racecadotril (1.5 mg per kg of body weight orally every eight hours) or placebo, in addition to oral rehydration solution The primary end point was the 48-h stool output (measured in grams); the total stool output, duration of diarrhea, and total intake of oral rehydration solution were also measured. The mean (±SE) 48-h stool output was 92±12 g per kg in the racecadotril group and 170±15 g per kg in the placebo group ($P<0.001$), a 46 percent reduction with racecadotril. The results were similar among the 73 boys with rotavirus infections. The total stool output was 157±27 g per kg in the racecadotril group and 331±39 g per kg in the placebo group ($P<0.001$). The median duration of diarrhea was significantly less ($P<0.001$) in the racecadotril group (28 h regardless of rotavirus status) than in the placebo group (72 and 52 h, resp., for rotavirus-pos. and rotavirus-neg. patients). The intake of oral rehydration solution was significantly lower in the racecadotril group than in the placebo group ($P<0.001$). Racecadotril was well tolerated; only seven patients taking racecadotril had adverse effects, which were all mild and transient. In young boys with acute watery diarrhea, racecadotril is an effective and safe treatment.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 33 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:555537 CAPLUS
DN 134:13176
TI Effects of chronic neutral endopeptidase inhibition in rats with cyclosporine-induced hypertension
AU Takeda, Yoshiyu; Inaba, Satoru; Furukawa, Kenji; Fujimura, Akio; Miyamori, Isamu; Mabuchi, Hiroshi
CS Second Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, 920, Japan
SO Journal of Hypertension (2000), 18(7), 927-933
CODEN: JOHYD3; ISSN: 0263-6352
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Cyclosporine (CysA), a potent immunosuppressant, is associated with hypertension and nephrotoxicity. Neutral endopeptidase (NEP) degrades vasoactive peptides, including the natriuretic peptides and endothelin-1 (ET-1). The present study was sone to determine whether or not the NEP inhibitor ecadotril prevents CysA-induced hypertension and to clarify the mechanisms responsible for the hypotensive effects of ecadotril. The chronic effects of ecadotril (30 mg/kg/) were studied on: blood pressure; the production of ET-1 and C-type natriuretic peptide (CNP); endothelial NO synthase (eNOS) activity; and the expression of mRNA for these substances in blood vessels of rats with CysA-induced hypertension. CysA (25 mg/kg/) given for 4 wk increased the blood pressure in rats. This increase was blunted by the coadministration of ecadotril. CysA increased plasma NEP activity. CysA increased the production of ET-1 and the expression of ET-1 mRNA without affecting CNP synthesis or endothelin-converting enzyme (ECE)-1 mRNA expression. CysA decreased eNOS activity and eNOS mRNA expression. Addition of the NEP inhibitor decreased the ET-1 synthesis and ET-1 mRNA and increased eNOS activity and eNOS mRNA. Vascular CNP synthesis and ECE-1 mRNA expression in rats treated with ecadotril alone

did not differ from those in rats treated with CysA and ecadotril. These results indicate that chronic NEP inhibition may prevent CysA-induced hypertension by decreasing local ET-1 synthesis and partly increasing vascular NO production
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 34 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:373741 CAPLUS
DN 133:114836
TI Intrarenal effects of ecadotril during acute volume expansion in dogs with congestive heart failure
AU Solter, Philip; Sisson, David; Thomas, William; Goetze, Leopold
CS University of Illinois, Urbana-Champaign, Urbana, IL, USA
SO Journal of Pharmacology and Experimental Therapeutics (2000), 293(3), 989-995
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Neutral endopeptidase 24.11 (NEP) inhibitors are known to have vascular, diuretic, and natriuretic effects that may be helpful in the treatment of congestive heart failure (CHF). Most NEP inhibitors may act principally through intrarenal mechanisms, which are not completely understood. The purpose of this study was to determine the principal renal effects of the NEP inhibitor ecadotril in dogs with progressive CHF induced by rapid ventricular pacing. Renal function was measured before, during, and after acute i.v. infusion of normal saline in a total of six dogs during normal cardiac function, early left ventricular dysfunction, and overt CHF. During overt CHF, each dog was treated with either ecadotril or placebo orally for 1 wk. Parameters measured included glomerular filtration rate, renal blood flow, urine output, sodium clearance, sodium fractional excretion, and proximal and distal sodium resorption. Ecadotril treatment resulted in increased urine output, sodium clearance, and renal sodium excretion relative to placebo treated controls. The principal intrarenal effect of ecadotril was decreased distal renal tubular sodium resorption. Both glomerular filtration rate and renal blood flow declined during overt CHF and were unaffected by ecadotril treatment. The results of this study are consistent with the principal action of ecadotril occurring by way of intrarenal events as opposed to changes in renal hemodynamics. The principal effect of ecadotril on distal tubular sodium resorption suggests that inhibition of NEP activity in the proximal renal tubules may allow increased binding of filtered atrial natriuretic peptide to natriuretic peptide receptor sites in the distal renal tubules and collecting ducts.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 35 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:347593 CAPLUS
DN 132:342657
TI Racecadotril
AU Matheson, Anna J.; Noble, Stuurt
CS Adis International Limited, Auckland, N. Z.
SO Drugs (2000), 59(4), 829-835
CODEN: DRUGAY; ISSN: 0012-6667
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review with 23 refs. Racecadotril is an oral enkephalinase inhibitor used in the treatment of acute diarrhea. It prevents the degradation of endogenous opioids (enkephalins), thereby reducing hypersecretion of water and electrolytes into the intestinal lumen. In a randomized double-blind

study in 6 adult volunteers with castor oil-induced diarrhoea, racecadotril significantly reduced stool weight and stool number in comparison with placebo. Similar results have been obtained in treating castor oil-induced diarrhoea in rats. Racecadotril was significantly more effective than placebo in randomized double-blind studies in adults or children with diarrhoea (of infectious origin or in adults with HIV infection). In well controlled trials, racecadotril had efficacy similar to that of loperamide and was generally as effective as loperamide-oxide. Racecadotril had a similar tolerability profile to placebo, and was better tolerated than loperamide, in adults and children with diarrhoea. It caused significantly less constipation after resolution of diarrhoea than loperamide.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 36 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:283163 CAPLUS
DN 133:187787
TI Acute, subchronic, and chronic toxicity of ecadotril in dogs
AU Maertins, Thomas; Von Keutz, Eckhard; Goetze, Leopold
CS Agriculture Division-Animal Health, Bayer Corporation, Merriam, KS, 66202, USA
SO American Journal of Veterinary Research (2000), 61(4), 425-429
CODEN: AJVRAH; ISSN: 0002-9645
PB American Veterinary Medical Association
DT Journal
LA English
AB To determine acute toxicity, ecadotril (2000 mg/kg) in a gelatin capsule was administered once to dogs. To determine subchronic and chronic toxicity, ecadotril was administered every day for 3 mo (50, 100, and 300 mg/kg) and for 12 mo (25, 50, and 100 mg/kg), resp. Dogs that received 1 dose of 2000 mg ecadotril/kg developed nonspecific clin. signs of toxicosis. Dogs that received 300 mg ecadotril/kg/day for 3 mo developed pronounced anemia, bone marrow suppression, and some evidence of liver impairment. There was no evidence of an effect accumulating over time, and reversibility of toxic effects was evident. Dogs that received ≤100 mg/kg/day for 3 or 12 mo tolerated treatment without apparent effect. The degree of acute toxicity of a single high dose of ecadotril in dogs was low. The no-observable-adverse-effect dose of ecadotril following daily oral administration was 100 mg/kg/day; repeated administration of 300 mg/kg/day revealed the hematopoietic system as the primary toxicol. target.

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 37 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:194724 CAPLUS
DN 133:68666
TI Short-term effects of ecadotril in dogs with induced congestive heart failure
AU Olivier, N. Bari; Kutas, Susan M.; Beals, Sue; Hanson, Beth; Windram, Soren
CS Department of Small Animal Clinical Sciences, Michigan State University, East Lansing, MI, 48824, USA
SO American Journal of Veterinary Research (2000), 61(3), 333-338
CODEN: AJVRAH; ISSN: 0002-9645
PB American Veterinary Medical Association
DT Journal
LA English
AB In the title animals, orally administered ecadotril reduced left-ventricular filling pressures by a mechanism that does not include a substantial diuretic effect. Ecadotril may be effective for alleviating

clin. signs in dogs with left-sided heart failure and may be particularly beneficial for use in dogs that are refractory to traditional diuretic therapy.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 38 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:173701 CAPLUS
DN 132:342604
TI An overview of clinical studies with racecadotril in adults
AU Lecomte, J. M.
CS Bioprojet, Paris, Fr.
SO International Journal of Antimicrobial Agents (2000), 14(1), 81-87
CODEN: IAAGEA; ISSN: 0924-8579
PB Elsevier Science Ireland Ltd.
DT Journal; General Review
LA English
AB A review with 18 refs. Since preclin. studies had indicated the potential efficacy and tolerability of racecadotril for the treatment of diarrhea in man, a series of studies was carried out to assess the clin. effects of racecadotril. These studies were also designed to evaluate whether racecadotril possessed the clin. properties that had been previously identified for an ideal agent to treat infectious diarrhea. The pure antisecretory action of racecadotril was confirmed in these clin. studies, as was the drug's rapid onset of action. The high therapeutic index of racecadotril was combined with a lack of effect on the central nervous system. Finally, racecadotril was found to be effective in treating acute diarrhea in double-blind studies against both placebo and the μ opiate receptor agonist, loperamide. The efficacy of racecadotril in acute diarrhea was not associated with adverse gastrointestinal effects, and its adverse events profile was similar to that of placebo. It was concluded that racecadotril offers a new approach to the treatment of diarrhea via its mechanism of action as a true antisecretory agent.

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 39 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:173695 CAPLUS
DN 132:342603
TI Racecadotril: a new approach to the treatment of diarrhea
AU Schwartz, J.-C.
CS Unite de Neurobiologie et Pharmacologie Moleculaire (U-109) de l'INSERM, Centre Paul Broca, Paris, 75014, Fr.
SO International Journal of Antimicrobial Agents (2000), 14(1), 75-79
CODEN: IAAGEA; ISSN: 0924-8579
PB Elsevier Science Ireland Ltd.
DT Journal; General Review
LA English
AB A review with 15 refs. Enkephalins Since enkephalins were discovered in 1975, it has become clear that they play an antisecretory role in the gastrointestinal tract. Hence a rational research program was directed at the development of a drug that would preserve these neurotransmitter peptides in the gut by preventing their inactivation. This research program has resulted in the development of the enkephalinase inhibitor, racecadotril. Preclin. studies have demonstrated the efficacy of racecadotril in two models of hypersecretory diarrhea: infusion of cholera toxin and castor oil-induced diarrhea. Moreover, unlike loperamide, racecadotril did not prolong transit time in the small intestine or colon. Further expts. have shown that racecadotril does not promote bacterial overgrowth in the small intestine. Racecadotril lacks any potential for neurotoxicity, and radiolabeled studies have demonstrated that the drug does not enter the brain after oral administration. No potential for

abuse or phys. dependence has been seen. It is concluded that racecadotril demonstrates specificity of antisecretory action on the gastrointestinal tract without any adverse effect on gastrointestinal motility, and that the results of the preclin. studies indicate the potential usefulness in the treatment of hypersecretory diarrhea in man.
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 40 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:51142 CAPLUS
DN 132:87974
TI Comparison of racecadotril and loperamide in children with acute diarrhea
AU Turck, D.; Berard, H.; Fretault, N.; Lecomte, J. M.
CS Hopital Jeanne de Flandre, Lille, 59037, Fr.
SO Alimentary Pharmacology and Therapeutics (1999), 13(Suppl. 6), 27-32
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB Methods A multicenter, parallel-group, double-blind, double-placebo study was carried out to compare the efficacy, tolerability, and safety of racecadotril and loperamide in children aged 2 to 10 yr who were suffering from acute diarrhea. Patients received racecadotril (1.5 mg/kg) or loperamide (0.03 mg/kg) three times daily plus matching placebo until recovery. Fifty-two children received racecadotril and 50 loperamide. Results Patients on racecadotril passed a mean (± S.E.M.) of 2.7±0.4 stools before recovery compared with 2.1±0.4 stools for loperamide. The duration of diarrhea was similar with both treatments. The incidence of adverse events was lower with racecadotril than with loperamide (11.5% vs. 22%), and significantly more patients on loperamide suffered from constipation (58% vs. 36.5%; P = 0.03). Moreover, significantly more children receiving loperamide required concomitant medication during the study (38% v 19.2%; P = 0.047). Measurement of abdominal circumference at the final consultation, 6 days after entry to the study, revealed no significant differences between treatments. Conclusions Racecadotril and loperamide were equally effective in treating acute diarrhea in these children, and racecadotril had a superior tolerability and safety profile.
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 41 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:51141 CAPLUS
DN 132:87973
TI Comparison of racecadotril and loperamide in adults with acute diarrhea
AU Vetel, J. M.; Berard, H.; Fretault, N.; Lecomte, J. M.
CS Centre Hospitalier, Le Mans, 72000, Fr.
SO Alimentary Pharmacology and Therapeutics (1999), 13(Suppl. 6), 21-26
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB A multicenter, randomized, double-blind, double-placebo, parallel-group study was carried out to compare the efficacy, tolerability, and safety of racecadotril (100 mg three times daily) and loperamide (2 mg after each diarrheic stool) in 157 adults with acute diarrhea. Patients were treated for 7 days or until recovery, if this took place earlier. Both groups of patients passed similar nos. (mean ± S.E.M.) of stools before recovery (3.5±0.5 for racecadotril vs. 2.9±0.4 for loperamide), and the duration of diarrhea (mean ± S.E.M.) was similar in both groups (14.9±2.0 h for racecadotril and 13.7±2.2 h for loperamide). Both treatments reduced the incidence of associated symptoms and signs during the study, and both were similarly well tolerated. However, more patients on

loperamide reported rebound constipation during treatment (18.7% vs. 9.8% with racecadotril). The enkephalinase inhibitor, racecadotril, and the intestinal transit inhibitor, loperamide, were similarly and rapidly effective in resolving the symptoms and associated signs of diarrhea.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 42 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:51140 CAPLUS
DN 132:87972
TI Racecadotril versus placebo in the treatment of acute diarrhea in adults
AU Hamza, H.; Ben Khalifa, H.; Baumer, P.; Berard, H.; Lecomte, J. M.
CS Taoufik Clinic, Tunis, Tunisia
SO Alimentary Pharmacology and Therapeutics (1999), 13(Suppl. 6), 15-19
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB A two-center, double-blind, parallel-group, randomized study was carried out to compare the efficacy and tolerability of racecadotril (100 mg three times daily) and placebo in 70 adult patients with acute diarrhea. An objective criterion of antisecretory activity, stool weight, was used. Racecadotril produced a significant (P = 0.025) decrease in stool weight during the first day of treatment compared with placebo, and was also associated with significantly fewer diarrheic stools than placebo after 1 day of treatment (P = 0.027). Racecadotril and placebo were equally well tolerated, and the frequency of symptoms and signs was similar in both groups after 4 days of treatment. Fewer patients on racecadotril suffered from abdominal distension following treatment (5.6% vs. 18.2% on placebo). Racecadotril acts rapidly to resolve acute diarrhea and has an incidence of adverse events similar to that of placebo.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 43 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:51139 CAPLUS
DN 132:343091
TI Effects of racecadotril and loperamide on bacterial proliferation and on the central nervous system of the newborn gnotobiotic piglet
AU Duval-Iflah, Y.; Berard, H.; Baumer, P.; Guillaume, P.; Raibaud, P.; Joulin, Y.; Lecomte, J. M.
CS Institut National de la Recherche Agronomique, Unite d'Ecologie et de Physiologie du Systeme Digestif, Centre de Recherche de Jouy, Jouy-en-Josas, 78352, Fr.
SO Alimentary Pharmacology and Therapeutics (1999), 13(Suppl. 6), 9-14
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB The effects of 4 days of oral administration of different doses of two drugs, an enkephalinase inhibitor (the antisecretory agent, racecadotril) and a μ-receptor agonist (loperamide), on intestinal growth of a bacterial nonpathogenic strain (Escherichia coli E 404) and on the central nervous system (CNS) were compared in newborn gnotobiotic piglets. The E. coli content of the proximal jejunum (segment S1) and the E. coli ratio of stomach:segment S1 were similar in the racecadotril (20 mg/kg b.d., n = 5) and control groups. In contrast, in the loperamide group (1 mg/kg b.d., n = 4), the E. coli content of segment S1 and the E. coli ratio stomach:S1 were both significantly higher than with racecadotril or control (P = 0.04 and 0.005, resp., for E. coli content; P = 0.05 and 0.03, resp., for stomach:S1). There were no clin. signs of neurotoxicity and no deaths with racecadotril given orally at a high dose of 130 mg/kg b.d. (n = 5) -

nearly 60 times the pediatric dosage. In contrast, an equivalent high dose of loperamide (5 mg/kg b.d.) resulted in death in three out of four piglets. In contrast to loperamide, racecadotril did not induce bacterial overgrowth and did not produce central neurotoxicity.

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 44 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:51138 CAPLUS
DN 132:343090
TI Racecadotril demonstrates intestinal antisecretory activity in vivo
AU Primi, M. P.; Bueno, L.; Baumer, P.; Berard, H.; Lecomte, J. M.
CS Department of Pharmacology, Institut National de la Recherche Agronomique, Toulouse, 31931, Fr.
SO Alimentary Pharmacology and Therapeutics (1999), 13(Suppl. 6), 3-7
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB The enkephalinase inhibitor racecadotril exhibits exptl. and clin. antidiarrheal activity without any effect on intestinal motility, suggesting selective antisecretory activity. The antisecretory effect of racecadotril was directly assessed in the present study. A jejunal, Thiry-Vella loop was created in dogs, and water and ion fluxes were evaluated during infusion of Tyrode's solution labeled with [14C]polyethylene glycol. Fluxes were determined in both the basal state and 5-6 h after commencement of a 2-h infusion of cholera toxin (0.4 μg/mL). Racecadotril (10 mg/kg) or vehicle was given orally with and without prior i.v. administration of naloxone (0.1 mg/kg) or phentolamine (0.2 mg/kg). Basal absorption remained unchanged following racecadotril administration; however, racecadotril decreased cholera toxin-induced water, sodium, and potassium hypersecretion. This antisecretory activity of racecadotril was suppressed by naloxone but not by phentolamine. This study demonstrates the antisecretory activity of racecadotril in relation to the protection of endogenous enkephalins.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 45 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:14186 CAPLUS
DN 132:44740
TI A randomized trial of ecadotril versus placebo in patients with mild to moderate heart failure: the U.S. ecadotril pilot safety study
AU O'Connor, Christopher M.; Gattis, Wendy A.; Gheorghiade, Mihai; Granger, Christopher B.; Gilbert, James; McKenney, James M.; Messineo, Frank C.; Burnett, John C.; Katz, Stuart D.; Elkayam, Uri; Kasper, Edward K.; Goldstein, Sidney; Cody, Robert J.; Massie, Barry M.
CS U.S. Ecadotril Investigators, Duke University Medical Center, Durham, NC, 27710, USA
SO American Heart Journal (1999), 138(6, Pt. 1), 1140-1148
CODEN: AHJOA2; ISSN: 0002-8703
PB Mosby, Inc.
DT Journal
LA English
AB In this small pilot study, ecadotril in doses of 50-400 mg twice daily was generally well tolerated and without severe short-term adverse effects in patients with mild to moderate heart failure.

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 46 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:579666 CAPLUS

09986629

DN 131:170171
TI Method for asymmetric preparation of 2-(mercaptomethyl)-3-phenylpropanoic acid derivatives for use in the synthesis of chiral pharmaceutically active principles
IN Binay, Patrice; Henry, Jean Christophe; Vidal, Virginie; Genet, Jean Pierre; Dellis, Philippe
PA Fournier Industrie et Sante s. A., Fr.
SO Fr. Demande, 23 pp.
CODEN: FRXXBL
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2772027	A1	19990611	FR 1997-15636	19971210
	FR 2772027	B1	20000204		
PRAI	FR 1997-15636		19971210		

OS CASREACT 131:170171
AB (R)- and (S)-RCH2CH(CO2H)CH2SAc [R = aryl] were prepared by asym. reduction of RCH:C(CO2H)CH2R1 [R1 = SAc, OAc, OH] and are useful in the preparation of (R)- and (S)-acetorphan. Thus, (S)-PhCH2CH(CO2H)CH2SAc was prepared by reduction of (Z)-PhCH:C(CO2H)CH2SAc in presence of 3% (R,R)-DiopRu(allyl)2 in MeOH. (Z)-PhCH:C(CO2H)CH2SAc was obtained by treating PhCHO with Me acrylate, ester hydrolysis, and reaction with HSAc.

L3 ANSWER 47 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:557717 CAPLUS
DN 131:170643
TI Method for producing an optically active phenylpropionic acid derivative
IN Suzuki, Takayuki; Hamada, Takayuki; Izawa, Kunisuke
PA Ajinomoto Co., Inc., Japan
SO Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 937710	A1	19990825	EP 1999-301004	19990211
	EP 937710	B1	20030416		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	ES 2196721	T3	20031216	ES 1999-301004	19990211
	JP 11315064	A2	19991116	JP 1999-34425	19990212
	CA 2262224	AA	19990816	CA 1999-2262224	19990216
	US 6031121	A	20000229	US 1999-249848	19990216
	US 6239305	B1	20010529	US 1999-455936	19991207
	US 2001014754	A1	20010816	US 2001-811592	20010320
	US 6339170	B2	20020115		
PRAI	JP 1998-32791	A	19980216		
	US 1999-249848	A1	19990216		
	US 1999-455936	A1	19991207		

OS CASREACT 131:170643; MARPAT 131:170643
AB Optically active N-[(S)-2-(acetylthiomethyl)-1-oxo-3-phenylpropyl] amino acid esters AcSCH2CH*(CH2Ph)CONHCHR1CO2R2 (R1 represents H or an optionally substituted amino acid side chain or protected amino acid side chain; R2 represents optionally substituted alkyl group or benzyl; * denotes an optionally active carbon atom) were prepared by subjecting optically active 2-hydroxymethyl-3-phenylpropionic acid and glycine esters to condensation, subsequently converting the hydroxyl group into an elimination group, and substituting the elimination group with an acetylthio group. Thus, (S)-2-hydroxymethyl-1-oxo-3-phenylpropionic acid

was prepared and treated with glycine benzyl ester tosylate salt, followed by reaction with methanesulfonyl chloride and potassium thioacetate, to afford N-[(S)-2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]glycine benzyl ester.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 48 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:374489 CAPLUS
DN 131:27367
TI Ecadotril. (S)-Acetorphan, sinorphan
AU Anon.
CS N. Z.
SO Drugs in R&D (1999), 1(4), 343-345
CODEN: DRDDFD; ISSN: 1174-5886
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review, with 9 refs., describing the pharmacodynamic effects of ecadotril, a neutral endopeptidase inhibitor currently undergoing trials for the treatment of hypertension and heart failure. Ecadotril, the (S)-enantiomer of acetorphan, is 2-3-fold more potent than the (R)-enantiomer, retorphan.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 49 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:226242 CAPLUS
DN 131:27719
TI Interaction between neutral endopeptidase and angiotensin-converting enzyme inhibition in rats with myocardial infarction: effects on cardiac hypertrophy and angiotensin and bradykinin peptide levels
AU Duncan, Ann-Maree; James, Gail M.; Anastasopoulos, Frank; Kladis, Athena; Briscoe, Todd A.; Campbell, Duncan J.
CS St. Vincent's Institute of Medical Research, Fitzroy, Australia
SO Journal of Pharmacology and Experimental Therapeutics (1999), 289(1), 295-303
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Combined inhibition of neutral endopeptidase 24.11 (NEP) and angiotensin-converting enzyme (ACE) is a candidate therapy for hypertension and cardiac failure. Given that NEP and ACE metabolize angiotensin (Ang) and bradykinin (BK) peptides, the authors investigated the effects of NEP inhibition and combined NEP and ACE inhibition on Ang and BK levels in rats with myocardial infarction. The authors administered the NEP inhibitor ecadotril (0, 0.1, 1, 10, and 100 mg/kg/day), either alone or together with the ACE inhibitor perindopril (0.2 mg/kg/day), by 12-hourly gavage from day 2 to 28 after infarction. Ecadotril increased urine cyclic GMP and BK-(1-9) excretion. Perindopril potentiated the effect of ecadotril on urine cyclic GMP excretion. Neither perindopril nor ecadotril reduced cardiac hypertrophy when administered sep., whereas the combination of perindopril and 10 or 100 mg/kg/day ecadotril reduced heart weight/body weight ratio by 10%. Administration of ecadotril to perindopril-treated rats decreased plasma Ang-(1-7) levels, increased cardiac BK-(1-9) levels, and increased Ang II levels in plasma, kidney, aorta, and lung. These data demonstrate interactions between the effects of NEP and ACE inhibition on remodeling of the infarcted heart and on Ang and BK peptide levels. Whereas increased cardiac BK-(1-9) levels may contribute to the reduction of cardiac hypertrophy, the reduction in plasma Ang-(1-7) levels and increase in Ang II

levels in plasma and tissues may compromise the therapeutic effects of combined NEP/ACE inhibition.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 50 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:103855 CAPLUS
DN 130:336244
TI Antiarrhythmic effect of hypoxic preconditioning is mediated by activation of μ- and δ-opioid receptors
AU Uskina, E. V.; Maslov, L. N.; Lishmanov, Y. B.
CS Department of Experimental Cardiology Institute of Cardiology, Siberian Division of the Russian Academy of Medical Science, Tomsk, Russia
SO Bulletin of Experimental Biology and Medicine (Translation of Byulleten Eksperimental'noi Biologii i Meditsiny) (1998), 125(3), 239-241
CODEN: BEXBAN; ISSN: 0007-4888
PB Consultants Bureau
DT Journal
LA English
AB Adaptation of rats to repetitive hypoxia leads a decrease in the severity and frequency of arrhythmias induced by epinephrine. Naloxone abolishes antiarrhythmic effect of adaptation. Activation of μ-and δ-opioid receptors is one of the important factors mediating antiarrhythmic effect of adaptation. I.v. administration of acetorphan, an enkephalinase inhibitor, produces statistically significant antiarrhythmic effect in the control group. Thus, the antiarrhythmic effect of hypoxic adaptation results from activation of μ-and δ-opioid receptors due to increased level of endogenous enkephalins.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 51 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:743857 CAPLUS
DN 130:105062
TI Effects of neutral endopeptidase inhibition and combined angiotensin converting enzyme and neutral endopeptidase inhibition on angiotensin and bradykinin peptides in rats
AU Campbell, Duncan J.; Anastasopoulos, Frank; Duncan, Ann-Maree; James, Gail M.; Kladis, Athena; Briscoe, Todd A.
CS St. Vincent's Institute of Medical Research, Fitzroy, 3065, Australia
SO Journal of Pharmacology and Experimental Therapeutics (1998), 287(2), 567-577
CODEN: JPETAB; ISSN: 0022-3565
PB Lippencott Williams & Wilkins
DT Journal
LA English
AB The combination of neutral endopeptidase 24.11 (NEP) and angiotensin converting enzyme (ACE) inhibition is a candidate therapy for hypertension and cardiac failure. Given that NEP and ACE metabolize angiotensin (Ang) and bradykinin (BK) peptides, we investigated the effects of NEP inhibition and combined NEP and ACE inhibition on the levels of these peptides. We administered the NEP inhibitor ecadotril (0, 0.1, 1, 10, 100 mg/kg per day), either alone or together with the ACE inhibitor perindopril (0.2 mg/kg per day), to rats by 12 hourly gavage for 7 days. Ecadotril produced diuresis, natriuresis, increased urine cyclic guanosine monophosphate and BK-(1-9) levels, increased Ang II and Ang I levels in plasma, and increased Ang I levels in heart. Perindopril reduced Ang II levels in kidney, and increased BK-(1-9) levels in blood, kidney and aorta. Combined NEP/ACE inhibition produced the summation of these effects of sep. NEP and ACE inhibition. In addition, perindopril potentiated the ecadotril-mediated diuresis, natriuresis and decrease in urine BK-(1-7)/BK-(1-9) ratio, which is an index of BK-(1-9) metabolism Moreover,

combined NEP/ACE inhibition increased Ang II levels in plasma and lung. These data indicate that summation of the effects of sep. NEP and ACE inhibition provides the basis for the therapeutic efficacy of their combination. Whereas potentiation by perindopril of the diuretic and natriuretic effects of ecadotril may contribute to the therapeutic effects, increased Ang II levels in plasma and lung may compromise the therapeutic effects of combined NEP/ACE inhibition.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 52 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:554394 CAPLUS
DN 129:298046
TI Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment
AU Saliba, Faouzi; Hagipantelli, Rachel; Misset, Jean-Louis; Bastian, Gerard; Vassal, Gilles; Bonnay, Marc; Herait, Patrice; Cote, Carole; Mahjoubi, Mondher; Mignard, Dominique; Cvitkovic, Esteban
CS Institut Gustave Roussy, Paul Brousse Hospital, Villejuif, 94804, Fr.
SO Journal of Clinical Oncology (1998), 16(8), 2745-2751
CODEN: JCONDN; ISSN: 0732-183X
PB W. B. Saunders Co.
DT Journal
LA English
AB This study investigated the pathophysiol. of irinotecan (CPT-11)-induced delayed-onset diarrhea and assessed the efficacy of combined antidiarrheal drugs in a phase II, prospective, successive-cohorts, open study. Patients with advanced colorectal cancer refractory to fluorouracil therapy received CPT-11 at 350 mg/m2 every 3 wk. The 1st cohort of patients explored for the mechanism of diarrhea received acetorphan (a new enkephalinase inhibitor) at 100 mg 3 times daily; the 2nd cohort received, in addition to acetorphan, loperamide at 4 mg 3 times daily. Before treatment, and if late diarrhea occurred, the patients underwent numerous clin. tests. Delayed-onset diarrhea occurred during the 1st 3 treatment cycles in 23 patients (82%). Electrolyte fecal measurements showed a neg. or small osmotic gap in 9 of 9 patients and an increased α1-antitrypsin clearance in 6 of 6 patients. There were no modifications in stool cultures or hormonal dysfunction. Four of 11 patients (36%) with delayed-onset diarrhea in the 1st cohort responded to acetorphan, whereas 9 of 10 patients (90%) responded to the combination of acetorphan and loperamide. CPT-11-induced delayed-onset diarrhea is caused by a secretory mechanism with an exudative component. Early combined treatment with loperamide and acetorphan seems effective in controlling the diarrheal episodes.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 53 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:540908 CAPLUS
DN 129:285546
TI Biosynthesis of an aminopiperidino metabolite of irinotecan [7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecine] by human hepatic microsomes
AU Haaz, Marie-Christine; Riche, Christian; Rivory, Laurent P.; Robert, Jacques
CS Institut Bergonie and Universite Victor Segalen Bordeaux 2, Bordeaux, 33076, Fr.
SO Drug Metabolism and Disposition (1998), 26(8), 769-774
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English

09986629

AB Irinotecan [7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecine] is a water-soluble analog of camptothecine used in the 2nd-line treatment of advanced colon cancer. Recently, we identified, in the plasma of patients and in human liver microsomal incubations, the presence of a new metabolite of irinotecan, 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecine (NPC), which is produced by cleavage of the distal piperidine ring of irinotecan. The kinetics of biotransformation of the lactone and carboxylate forms of irinotecan into NPC were studied using human liver microsomes. The formation of NPC was characterized by the following parameters: KM = 48.2 ± 6.8 and 273 ± 122 μM and Vmax = 74.1 ± 4.9 and 78.6 ± 27.7 pmol/min/mg of protein for the lactone and carboxylate forms of irinotecan, resp. Interestingly, there was no formation of NPC from 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecine, a major metabolite of irinotecan that has an open distal piperidine ring and could be considered a possible metabolic precursor of NPC. The transformation of irinotecan into NPC was found to be catalyzed principally by cytochrome P 450 (CYP) 3A, based on 3 key results, as follows: (i) the CYP3A-selective inhibitors ketoconazole (1 μM) and troleandomycin (100 μM) inhibited NPC formation by 99 and 100%, resp.; (ii) of a series of microsomal prepns. from transfected lymphoblastoid cells expressing specific CYPs, only those from CYP3A4 cDNA-transfected cells transformed irinotecan into NPC; and (iii) incubations with 15 individual prepns. of human liver microsomes yielded highly significant correlations between the formation of NPC and both immunoreactivity with anti-CYP3A antibodies and testosterone 6β-hydroxylation (an activity specifically mediated by CYP3A). The effects of 11 drugs (used at 100 μM) on this metabolism were studied with irinotecan lactone (25 μM). Although ondansetron, loperamide, and racecadotril inhibited this pathway by 75, 95, and 95%, resp., the concns. used may not be clin. achievable. However, significant inhibition by ketoconazole and troleandomycin indicates that NPC formation in patients may be influenced by coadministration of drugs with known anti-CYP3A activities.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 54 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:413027 CAPLUS
DN 129:144784
TI The involvement of the opioidergic system in the antinociceptive mechanism of action of antidepressant compounds
AU Gray, A. M.; Spencer, P. S. J.; Sewell, R. D. E.
CS Division of Pharmacology, The Welsh School of Pharmacy, UWC, Cardiff, Cardiff, CF1 3XF, UK
SO British Journal of Pharmacology (1998), 124(4), 669-674
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton Press
DT Journal
LA English
AB 1 Debate exists as to the nature of antidepressant-induced antinociception. It is unclear whether antidepressants are inherently antinociceptive, are able to potentiate opioid antinociception or both. We have used the acetic acid induced abdominal constriction assay in mice to investigate antidepressant-induced antinociception. 2 All the antidepressants tested (s.c.) produced dose-dependent protection against acetic acid-induced abdominal constriction. Similarly, morphine and aspirin were also effective antinociceptive agents in this nociceptive assay. 3 Opioid antagonists, naloxone (0.5 mg kg-1, s.c.) and naltrindole (1 mg kg-1, s.c.), shifted the dose-response relationships to the right for each of the antidepressant agents (dothiepin, amitriptyline, sibutramine, (+)-oxaprotiline and paroxetine). In this context the naloxone dose-ratios were 1.95, 3.90, 2.32, 4.50 and 2.65, with

naltrindole dose-ratios of 4.36, 17.00, 4.28, 11.48 and 2.65 were obtained, resp. Naloxone also shifted the morphine dose-response relation to the right, by a factor of 2.62, while naltrindole had no effect upon morphine antinociception. Aspirin antinociception remained unaffected by both opioid antagonists. 4 The enkephalin catabolism inhibitor acetorphan, by itself, produced no activity in this test at a dose of 10 mg kg-1 (s.c.). However, at higher doses, acetorphan produced a linear dose-response relation against acetic acid-induced abdominal constriction. 5 When acetorphan was administered before either the antidepressants or morphine, there was a clear potentiation of the antidepressant- or morphine-induced antinociception. However, acetorphan had no effect on aspirin antinociception. 6 Since neither of the opioid antagonists were able to attenuate, nor was acetorphan able to potentiate, aspirin antinociception, we concluded that the mechanism of antidepressant-induced antinociception is different from that of the non-steroidal anti-inflammatory drugs. 7 These data are consistent with the view that antidepressants may induce endogenous opioid peptide release, as shown by the acetorphan study. In this context, the ability of naltrindole to displace the antidepressant dose-response relation to the right without affecting morphine antinociception, implicates the δ-opioid receptor and endogenous opioid peptides in antidepressant-induced antinociception.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 55 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:384115 CAPLUS
DN 129:156687
TI Effects of a neutral endopeptidase inhibitor, BP1.02, on the development of deoxycorticosterone acetate-salt hypertension in kininogen-deficient Brown Norway Katholiek rats
AU Nakajima, S.; Majima, M.; Ito, H.; Hayashi, I.; Yajima, Y.; Katori, M.
CS Department of Internal Medicine, Kitasato University School of Medicine, Kanagawa, 228-0855, Japan
SO International Journal of Tissue Reactions (1998), 20(2), 45-56
CODEN: IJTEDP; ISSN: 0250-0868
PB Bioscience Ediprint Inc.
DT Journal
LA English
AB The nature of all of the peptides critical to the mechanism(s) of the antihypertensive action of neutral endopeptidase (NEP) inhibitors is still unclear, but bradykinin is thought to be one such peptide. This study was designed to assess the effectiveness of an NEP inhibitor in deoxycorticosterone acetate (DOCA)-salt treated kininogen-deficient Brown Norway Katholiek (BN-Ka) rats. Oral administration of BP1.02 (10-100 mg/kg), an NEP inhibitor, increased urine volume and urinary sodium excretion in a dose-dependent manner in anesthetized Sprague-Dawley rats. DOCA-salt hypertension was induced in both BN-Ka and Brown Norway Kitasato (BN-Ki) rats after left nephrectomy. The development of DOCA-salt hypertension in normal BN-Ki rats was prevented, and that in BN-Ka rats was also significantly reduced, by an 8-day administration of BP1.02. When BP1.02 was administered for 5 wk, the high blood pressure of DOCA-salt treated BN-Ka rats was markedly lowered, and their heart wts. were reduced. These results suggest that kinins play no role in the antihypertensive effect of this inhibitor and that other factors may be involved in this effect.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

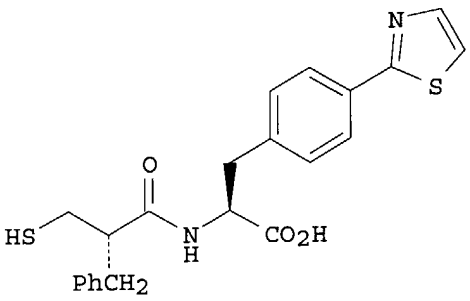
L3 ANSWER 56 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:372650 CAPLUS
DN 129:41415
TI Preparation of thiol-containing peptide derivatives with metallopeptidase

09986629

inhibitory activity
IN Santangelo, Francesco; Fantucci, Mario; Semeraro, Claudio; Pellacini, Franco; Romagnano, Stefano; Norcini, Gabriele
PA Zambon Group S.p.A., Italy
SO U.S., 12 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5760241	A	19980602	US 1996-774298	19961224
	US 5994539	A	19991130	US 1997-993567	19971218
PRAI	WO 1996-EP251	A	19960123		
	US 1996-774298	A3	19961224		

OS MARPAT 129:41415
GI



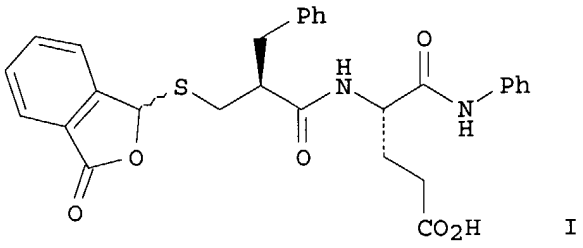
I

AB Title compds. RS(CH2)nCHR1CO(NHCHR2CO)mNHCH(CH2R3)CO2R4 [I; R = R = H, R5CO; R1, R2 = independently H, (un)branched C1-6 alkyl, aryl, C1-6 alkyl-aryl; aryl = (un)substituted Ph, PhC6H4, naphthyl, 5-6 membered aromatic heterocycle; R3 = Ph substituted with (un)substituted Ph or 5-6 membered aromatic heterocycle; R4 = H, C1-4 alkyl, CH2Ph; R5 = (un)branched C1-4 alkyl, Ph; m = 0-1; n = 0-1; with the proviso that when R3 = PhC6H4 and R1 = alkylaryl, the alkyl portion of the alkylaryl group is a straight alkyl moiety] and stereoisomers and pharmaceutically acceptable salts thereof, processes for their preparation and pharmaceutical compns. which contain them as active ingredients are described. The compds. I are endowed with a mixed angiotensin-converting enzyme (ACE)-inhibitory and neutral endopeptidase (NEP)-inhibitory activity and are useful in the treatment of cardiovascular diseases. Thus, peptide coupling of (S)-PhCOSCH2CH(CH2Ph)CO2H with 4-(2-thiazolyl)-L-phenylalanine Me ester dihydrochloride, followed by saponification with NaOH in aqueous EtOH gave title compound II. II inhibited ACE with IC50 = 3.2 nm and NEP with IC50 = 1.8 nM in an in vitro assay.
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 57 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:274553 CAPLUS
DN 129:16351
TI New orally active enkephalinase inhibitors: their synthesis, biological activity, and analgesic properties
AU Senokuchi, Kazuhiko; Nakai, Hisao; Nagao, Yuuki; Sakai, Yasuhiro; Katsube, Nobuo; Kawamura, Masanori

09986629

CS Department of Medicinal Chemistry, Minase Research Institute, Ono Pharmaceutical Co., Ltd., Osaka, 618, Japan
SO Bioorganic & Medicinal Chemistry (1998), 6(4), 441-463
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
GI



I

AB A series of (4S)-4-[(2S)-benzyl-3-mercaptopropionylamino]-4-(N-phenylcarbamoyl)-butyric acids has been identified as potent systemically active enkephalinase inhibitors. Structure-activity relationships (SAR) are discussed. Further chemical modification of the inhibitors was carried out in order to identify the inhibitors which are orally active in an animal model. Their analgesic effects after oral administration were evaluated. Compds. of particular interest are the prodrug-like analogs, including I (ONO-9902). Evaluation of I using the bradykinin-induced nociceptive biting-like and AcOH induced writhing responses indicated a 30 mg/kg ED50 and 10 mg/kg as the min. ED values in oral administration.

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 58 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:268482 CAPLUS
DN 128:321930
TI Preparation of β-thiopropionylamino acid derivatives as β-lactamase inhibitors
IN Bateson, John Hargreaves; Best, Desmond John; Clarke, Brian Peter; Gilpin, Martin Leonard; Witty, David R.; et al.
PA Smithkline Beecham Plc, UK; Bateson, John Hargreaves; Best, Desmond John; Clarke, Brian Peter; Gilpin, Martin Leonard
SO PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9817639	A1	19980430	WO 1997-EP5709	19971010
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9850501	A1	19980515	AU 1998-50501	19971010
EP 934262	A1	19990811	EP 1997-913147	19971010

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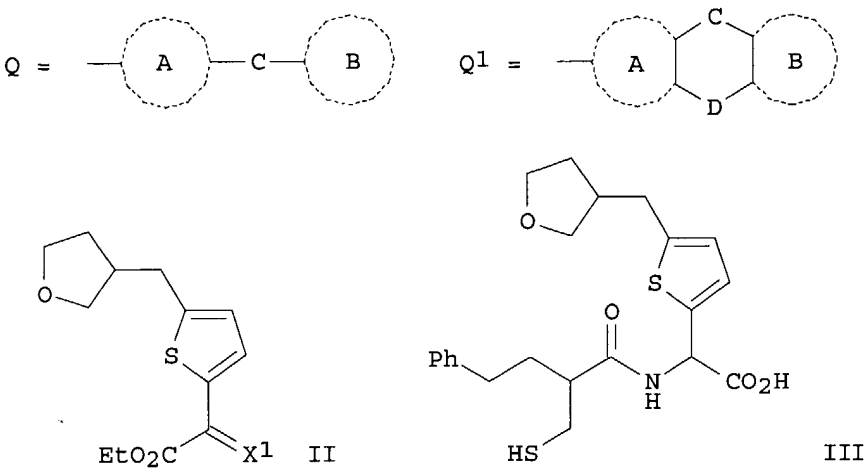
R: BE, CH, DE, ES, FR, GB, IT, LI, NL

	JP 2001502345	T2	20010220	JP 1998-518931	19971010
	US 6156774	A	20001205	US 1999-284098	19990407
PRAI	GB 1996-21692	A	19961017		
	GB 1997-4581	A	19970305		
	GB 1997-16212	A	19970731		
	WO 1997-EP5709	W	19971010		

OS MARPAT 128:321930

GI



AB Title mercapto amino acid derivs. R4SCR5R6CHR3CONR2CHR1CO2R [I; R = H, salt-forming cation of in vivo hydrolyzable ester-forming group; R1 = Q, Q1; ring A = monocyclic aryl or heteroaryl ring; ring B = monocyclic aryl, alicyclic, or heterocyclic ring; C, D = Zp(CR8CR9)q, (CR8CR9)qZp; p = 0, 1, q = 0-3 provided that p + q ≠ 0 in C; R8, R9 = H, (C1-6)alkyl; CR8R9 = O; Z = O, NR10, S(O)x; R10 = H, (C1-6)alkyl. aryl(C1-6)alkyl; x = 0-2; wherein C and D are linked ortho to one another on each of the rings A and B in Q1; R2 = H, (C1-6)alkyl, aryl(C1-6)alkyl; R3 = H, (C1-6)alkyl substituted by 0-3 halo atoms, (C3-7)cycloalkyl, fused aryl(C3-7)cycloalkyl, (C3-7)cycloalkyl(C2-6)alkyl, (C2-6)alkenyl, (C2-6)alkynyl, aryl, aryl-(CH2)m-X-(CH2)n, heterocyclyl, heterocyclyl-(CH2)m-X-(CH2)n; m = 0-3; n = 1-3; X = O, S(O)x, bond; R4 = H or in vivo hydrolyzable acyl; R5, R6 = H, (C1-6)alkyl; R5R6 = (CH2)2-5] for use in treatment of bacterial infections in humans or animals by administration in combination with a β-lactam antibiotic. Thus, lithiation of thiophene and alkylation with 3-(bromomethyl)tetrahydrofuran gave 2-(tetrahydrofuran-3-ylmethyl)thiophene, which underwent lithiation and acylation with Et oxalyl chloride to give oxoacetate II (X1 = O). II (X1 = O) was converted into hydroxyiminoacetate II (X1 = NOH), reduced in situ to the corresponding amine, acylated with 2-(acetylthio)4-phenylbutanoic acid (preparation given), and saponified to give desired title compound III. III and related mercaptopropionyl derivs. inhibited Bacteroides fragilis CfiA metallo-β-lactamase with IC50 <1 μM. Compound III inhibited Bacteroides fragilis 262 strain, which produces CfiA metallo-β-lactamase, alone with MIC >256 μg/mL, but with MIC 16 μg/mL in the presence of 8 μg/mL meropenem.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 59 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:137789 CAPLUS
DN 128:239215
TI Effect of ecadotril, a neutral endopeptidase inhibitor, on myocardial hypertrophy in the rat aortic insufficiency model
AU Kimura, Masahiko; Umemura, Kazuo; Ohashi, Kyoichi; Nakashima, Mitsuyoshi
CS Department of Clinical Pharmacology and Pharmacology, Hamamatsu University School of Medicine, Hamamatsu, 431-31, Japan
SO Canadian Journal of Cardiology (1998), 14(1), 63-68
CODEN: CJCAEX; ISSN: 0828-282X
PB Pulsus Group
DT Journal
LA English
AB Cardiac hypertrophy develops to compensate for hemodynamic overload of the myocardium. However, cardiac hypertrophy itself poses a serious risk to patients with heart failure. Whether natriuretic peptides enhanced by ecadotril, a neutral endopeptidase inhibitor, suppress the increase of left ventricular mass in the rat aortic insufficiency model was investigated. Ecadotril suppressed the increase of the left ventricular mass without affecting blood pressure (710.9±15.6 mg in the group treated with ecadotril and 865.0±27.3 mg in the control group, $P<0.01$). Although the increase of atrial natriuretic peptide in the left ventricle was trivial and did not reach statistical significance (406.5±62.2 pg/mg in the ecadotril-treated group vs. 269.8±35.7 pg/mg in the control group), urinary cGMP excretion was greater in the group given ecadotril than in the control group (10.6±2.5 pmol/mL and 1.7±0.6 pmol/mL, resp., $P<0.01$). Plasma angiotensin II concentration also decreased in the group treated with ecadotril compared with the control group (116.6±25.4 pg/mL vs. 358.7±98.7 pg/mL, $P<0.05$). In conclusion, ecadotril suppressed the increase of left ventricular mass in the overloaded heart. In ecadotril-treated rats, cGMP synthesis was augmented and angiotensin II concentration was reduced.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 60 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:632810 CAPLUS
DN 127:322795
TI Slow-release compositions of hardly soluble drugs
IN Tsukada, Takayuki; Fujii, Toshiro; Suzuki, Yusuke; Ogura, Toshihiro
PA Shionogi and Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 09249557	A2	19970922	JP 1996-58114	19960314
PRAI	JP 1996-58114		19960314		

AB Preparation of slow-release compns. of hardly soluble drugs are claimed. Ecadotril-containing cores were coated with (A) a composition contg hydroxypropylmethyl cellulose, sugar, talc and water, (B) an enteric layer containing hydroxypropylmethyl cellulose stearate succinate, talc, ammonia and water, (C) the A composition, (D) the B composition, (E) a composition containing ecadotril, mannitol, hydroxypropylmethyl cellulose and water. The prepared granules were filled into number 3 capsules.

L3 ANSWER 61 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:623026 CAPLUS
DN 127:225322

09986629

TI Rapid-release microdispersible ecadotril preparation
IN Tsukada, Takayuki; Suzuki, Yusuke; Ogura, Toshihiro
PA Shionogi & Co., Ltd., Japan; Tsukada, Takayuki; Suzuki, Yusuke; Ogura, Toshihiro
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9733571	A1	19970918	WO 1997-JP773	19970312
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9719397	A1	19971001	AU 1997-19397	19970312
	EP 914822	A1	19990512	EP 1997-907281	19970312
	R: DE, FR, GB, IT, NL				
	US 2002028248	A1	20020307	US 1999-142572	19990129
PRAI	JP 1996-58113	A	19960314		
	WO 1997-JP773	W	19970312		

AB A process for producing a rapid-release microdispersible ecadotril preparation comprises the step of treating a mixture of ecadotril and a disintegrator with a wettability improver or the step of combining ecadotril treated with a wettability improver and a disintegrator.

L3 ANSWER 62 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:618094 CAPLUS
DN 127:263058
TI Preparation of novel amide bond-containing thiol derivatives as endothelin converting enzyme inhibitors
IN Deprez, Pierre; Dumas, Jacques; Fournie-Zaluski, Marie-Claude; Guillaume, Jacques; Roques, Bernard Pierre
PA Roussel-UCLAF, Fr.; Institut National de la Sante et de la Recherche Medicale (INSERM)
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9732874	A1	19970912	WO 1997-FR367	19970303
	W: AU, BR, CA, CN, HU, IL, JP, KR, MX, NO, PL, RU, TR, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FR 2745571	A1	19970905	FR 1996-2672	19960304
	FR 2745571	B1	19980619		
	CA 2248187	AA	19970912	CA 1997-2248187	19970303
	AU 9719306	A1	19970922	AU 1997-19306	19970303
	AU 724686	B2	20000928		
	EP 888341	A1	19990107	EP 1997-907157	19970303
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	CN 1218467	A	19990602	CN 1997-194380	19970303
	BR 9707931	A	19990727	BR 1997-7931	19970303
	JP 2000507220	T2	20000613	JP 1997-531511	19970303
	RU 2203661	C2	20030510	RU 1998-118049	19970303
	NO 9804047	A	19981103	NO 1998-4047	19980903
	US 6136842	A	20001024	US 1999-142286	19990112
PRAI	FR 1996-2672	A	19960304		

WO 1997-FR367 W 19970303
OS MARPAT 127:263058
AB Thiol derivs. HS(CH2)nCH(CH2R1)CONHCHR2A (n = 0, 1; R1 = substituted Ph or biphenyl; R2 = H, substituted benzyl, phenylthiomethyl, or indolylmethyl; A = carboxy or a salt, ester, or amide, tetrazolyl, or substituted alkyl) were prepared as endothelin converting enzyme (ECE) inhibitors. Thus, N-[3-(3-bromophenyl)-2-(mercaptomethyl)-1-oxopropyl]-L-tryptophan was prepared via a 6-step procedure starting from Me 2-(dimethylamino)propanoate, 3-bromobenzyl bromide, thioacetic acid, and L-tryptophan. The product was assayed for ECE inhibitor activity (CI50 = 20 nM).

L3 ANSWER 63 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:563102 CAPLUS
DN 127:220985
TI Beta-thiopropionyl-amino acid derivatives and their use as beta-lactamase inhibitors
IN Bateson, John Hargreaves; Witty, David R.; Gasson, Brian Charles; Best, Desmond John; Payne, David John
PA Smithkline Beecham PLC, UK; Bateson, John Hargreaves; Witty, David R.; Gasson, Brian Charles; Best, Desmond John; Payne, David John
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9730027	A1	19970821	WO 1997-EP516	19970203
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2245830	AA	19970821	CA 1997-2245830	19970203
	AU 9717669	A1	19970902	AU 1997-17669	19970203
	EP 900197	A1	19990310	EP 1997-903220	19970203
	R: BE, CH, DE, ES, FR, GB, IT, LI, NL				
	JP 2000506120	T2	20000523	JP 1997-528946	19970203
	US 6048852	A	20000411	US 1999-125245	19990113
PRAI	GB 1996-2860	A	19960213		
	GB 1996-10907	A	19960524		
	GB 1996-19147	A	19960913		
	WO 1997-EP516	W	19970203		

OS MARPAT 127:220985
AB Amino acid derivs. R4SCR5R6CHR3CONR2CHR1CO2R [R = H, a salt forming cation or an in vivo hydrolyzable ester-forming group; R1 = H, alkyl optionally substituted by up to three halogen atoms or by a mercapto, alkoxy, hydroxy, amino, nitro, carboxy, alkylcarbonyloxy, alkoxycarbonyl, formyl or alkylcarbonyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, or heterocyclylalkyl; R2 = H, alkyl, or arylalkyl; R3 = H, alkyl optionally substituted by up to three halogen atoms, cycloalkyl, fused arylcycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, or heterocyclylalkyl; R4 = H or an in vivo hydrolyzable acyl group; R5, R6 = H, alkyl or R5R6 = di- to pentamethylene] were prepared as beta-lactamase inhibitors. Pharmaceutical compns. which comprise the title compds. together with a β-lactam antibiotic in a synergistically effective amount are claimed. Thus, N-[2'-benzyl-3'-mercaptopropionyl]-D-phenylglycine was prepared and assayed

for antibacterial activity (min. inhibitory concentration = >128 μg/mL). The min. inhibitory concentration of meropenem was 32 μg/mL in the presence of 8 μg/mL the above synthetic compound

L3 ANSWER 64 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:556063 CAPLUS
DN 127:149408
TI Preparation of N-mercaptoacyl alanine derivatives with metallopeptidase (ACE/NEP) inhibitory activity
IN Pellacini, Franco; Romagnano, Stefano; Norcini, Gabriele; Santangelo, Francesco; Semeraro, Claudio
PA Zambon Group S.P.A., Italy; Pellacini, Franco; Romagnano, Stefano; Norcini, Gabriele; Santangelo, Francesco; Semeraro, Claudio
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9724341	A1	19970710	WO 1996-EP5496	19961209
	W: AU, CA, CN, CZ, HU, KR, MX, NO, SI, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2241452	AA	19970710	CA 1996-2241452	19961209
	AU 9713691	A1	19970728	AU 1997-13691	19961209
	AU 706978	B2	19990701		
	EP 883612	A1	19981216	EP 1996-943903	19961209
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
	CN 1268945	A	20001004	CN 1996-199355	19961209
	CN 1108295	B	20030514		
	ZA 9610819	A	19970624	ZA 1996-10819	19961220
	US 6166051	A	20001226	US 1998-91415	19980623
PRAI	IT 1995-MI2772	A	19951228		
	WO 1996-EP5496	W	19961209		

OS MARPAT 127:149408
AB Compds. of formula RCH2CHR1CONHCH(CH2R3)CO2R2 [I; R = SH, R4COS convertible in the organism to SH group; R1 = straight or branched C2-4alkyl, (un)substituted aryl or aryl-C1-6alkyl; R2 = H, straight or branched C1-4 alkyl, benzyl; R3 = (un)substituted 5 or 6 membered aromatic heterocyclic group containing 1-2 N, O, S atoms optionally substituted with a Ph group, provided that R3 is not and imidazolyl or indolyl group; R4 = straight or branched C1-4 alkyl, phenyl] and pharmaceutical acceptable salts thereof, which are endowed with a dual ACE-inhibitory and NEP-inhibitory activity and are useful in the treatment of cardiovascular diseases, are prepared Thus, coupling of PhCOSCH2CH(CH2Ph)CO2H with (4-thiazolyl)-L-alanine Me ester, followed by hydrolysis gave mercaptoacyl alanine derivative HSCH2CH(CH2Ph)CO-(S)-NHCH(CH2R5)CO2H (II) (R5 = 4-thiazolyl). Compds. II (R5 = 4-thiazolyl) and II (R5 = 2-thienyl) showed IC50 of 12 and 6.5 nM, resp., against angiotensin converting enzyme (vs. 99 and 4.6 nM for thiorphan and captopril, resp.) and IC50 of 4.7 and 5.5 nM, resp., against neutral endopeptidase enzyme (vs. 18 nM and not active for thiorphan and captopril, resp.).

L3 ANSWER 65 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:547308 CAPLUS
DN 127:149407
TI Preparation of N-mercaptoacyl phenylalanine derivatives with metallopeptidase inhibitory activity
IN Pellacini, Franco; Fantucci, Mario; Norcini, Gabriele; Romagnano, Stefano; Santangelo, Francesco; Semeraro, Claudio

09986629

PA Zambon Group S.P.A., Italy; Pellacini, Franco; Fantucci, Mario; Norcini, Gabriele; Romagnano, Stefano; Santangelo, Francesco; Semeraro, Claudio

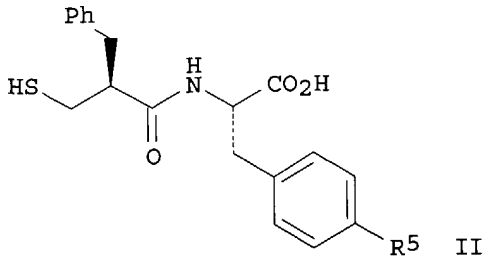
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9724342	A1	19970710	WO 1996-EP5663	19961217
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2241414	AA	19970710	CA 1996-2241414	19961217
	AU 9713018	A1	19970728	AU 1997-13018	19961217
	AU 713156	B2	19991125		
	EP 877740	A1	19981118	EP 1996-944583	19961217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
	CN 1206411	A	19990127	CN 1996-199354	19961217
	CN 1071325	B	20010919		
	BR 9612373	A	19990713	BR 1996-12373	19961217
	JP 2000502687	T2	20000307	JP 1997-524001	19961217
	IL 124915	A1	20011031	IL 1996-124915	19961217
	EE 3766	B1	20020617	EE 1998-192	19961217
	SK 282977	B6	20030109	SK 1998-889	19961217
	ZA 9610891	A	19970627	ZA 1996-10891	19961223
	BG 63942	B1	20030731	BG 1998-102553	19980618
	NO 9802977	A	19980827	NO 1998-2977	19980626
	HK 1018008	A1	20020426	HK 1999-103110	19990720
PRAI	IT 1995-MI2773	A	19951228		
	WO 1996-EP5663	W	19961217		

OS MARPAT 127:149407

GI



II

AB

Compds. of formula RCH2CHR1CONHCH(CH2R3)CO2R2 [I; R = SH, R4COS convertible in the organism to SH group; R1 = straight or branched C2-4 alkyl, (un)substituted aryl or aryl-C1-6 alkyl; R2 = H, straight or branched C1-4 alkyl, benzyl; R3 = (un)substituted Ph group substituted by a 5 or 6 membered aromatic heterocyclic group containing 1-2 N, O, S atoms; R4 = straight or branched C1-4 alkyl, phenyl] and pharmaceutical acceptable salts thereof, which are endowed with a dual ACE-inhibitory and NEP-inhibitory activity and are useful in the treatment of cardiovascular

diseases, are prepared Thus, coupling of (S)-PhC(O)SCH2CH(CH2Ph)CO2H with 4-(2-thiazolyl)-L-Phe-OMe dihydrochloride, followed by hydrolysis gave mercaptoacyl phenylalanine derivative II (R5 = 2-thiazolyl). Compds. II (R5 = 2-thiazolyl) and II (R5 = thienyl) showed IC50 of 3.2 and 1.6 nM, resp., against angiotensin converting enzyme (vs. 99 and 4.6 nM for thiorphan and captopril, resp.) and IC50 of 1.8 and 0.6 nM, resp., against neutral endopeptidase enzyme (vs. 18 nM and not active for thiorphan and captopril, resp.).

L3 ANSWER 66 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:542428 CAPLUS
DN 127:220983
TI Asymmetric synthesis of S-acylated derivatives of 2-mercaptomethyl-3-phenylpropanoic acid and their use in the synthesis of N-(mercaptoacyl) amino acids
IN Danvy, Denis; Monteil, Thierry; Duhamel, Pierre; Duhamel, Lucette; Lecomte, Jeanne-Marie; Schwartz, Jean-Charles
PA Societe Civile Bioprojet, Fr.
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729086	A1	19970814	WO 1997-FR218	19970204
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FR 2744446	A1	19970808	FR 1996-1360	19960205
	FR 2744446	B1	19980417		
	EP 820439	A1	19980128	EP 1997-904485	19970204
	EP 820439	B1	20000503		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11503470	T2	19990326	JP 1997-528218	19970204
	AT 192433	E	20000515	AT 1997-904485	19970204
	ES 2146981	T3	20000816	ES 1997-904485	19970204
	PT 820439	T	20001031	PT 1997-904485	19970204
	US 6013829	A	20000111	US 1997-930734	19971126
	GR 3033843	T3	20001031	GR 2000-401544	20000630
PRAI	FR 1996-1360	A	19960205		
	WO 1997-FR218	W	19970204		

OS MARPAT 127:220983
AB A method for the asym. synthesis of 2-mercaptomethyl-3-phenylpropanoic acid S-acyl derivs. PhCH2CH(CH2SR1)CO2H (R1 = acyl) is disclosed. The acyl derivs. were used to synthesize N-(mercaptoacyl) amino acids. Thus, (R)-2-(acetylthiomethyl)-3-phenylpropanoic acid (I) was prepared by reduction of di-Me benzylmalonate, monoacetylation, oxidation and saponification to give the hydroxy acid, and thioacylation with thioacetic acid using a Mitsunobu reaction. Coupling of I with benzyl glycinate afforded benzyl (R)-N-[2-(acetylthiomethyl)-3-phenylpropanoyl]glycinate.

L3 ANSWER 67 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:499121 CAPLUS
DN 127:171607
TI Medical use of an ACE inhibitor for treatment of dyspeptic symptoms
IN Fandriks, Lars; Pettersson, Anders
PA Astra AB (Publ), Swed.; Fandriks, Lars; Pettersson, Anders
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent

09986629

LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9726014	A1	19970724	WO 1996-SE1733	19961220
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2240199	AA	19970724	CA 1996-2240199	19961220
	AU 9713237	A1	19970811	AU 1997-13237	19961220
	AU 710846	B2	19990930		
	EP 876158	A1	19981111	EP 1996-944722	19961220
	EP 876158	B1	20020612		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	CN 1207685	A	19990210	CN 1996-199635	19961220
	CN 1090031	B	20020904		
	BR 9612483	A	19990713	BR 1996-12483	19961220
	JP 2001501908	T2	20010213	JP 1997-525898	19961220
	NZ 325973	A	20010525	NZ 1996-325973	19961220
	EE 3517	B1	20011015	EE 1998-203	19961220
	IL 125195	A1	20011125	IL 1996-125195	19961220
	AT 218885	E	20020615	AT 1996-944722	19961220
	PT 876158	T	20021031	PT 1996-944722	19961220
	ES 2175182	T3	20021116	ES 1996-944722	19961220
	SK 282781	B6	20021203	SK 1998-879	19961220
	RU 2203092	C2	20030427	RU 1998-113650	19961220
	ZA 9700083	A	19970715	ZA 1997-83	19970106
	US 5977159	A	19991102	US 1997-793059	19970213
	NO 9803234	A	19980714	NO 1998-3234	19980714
	HK 1014870	A1	20020906	HK 1999-100001	19990104
PRAI	SE 1996-120	A	19960115		
	WO 1996-SE1733	W	19961220		

AB A method for the prophylaxis and treatment of dyspeptic symptoms of unknown origin using ACE inhibitors, as well as a pharmaceutical preparation comprising these compds., are disclosed. A case report showing efficacy of enalapril is included.

L3 ANSWER 68 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:475526 CAPLUS
DN 127:156230
TI The transformation of irinotecan (CPT-11) to its active metabolite SN-38 by human liver microsomes. Differential hydrolysis of the lactone and carboxylate forms.
AU Haaz, Marie-Christine; Rivory, L. P.; Riche, Christian; Robert, J.
CS Institut Bergonie and University of Bordeaux II, 180 rue de Saint-Genes, Bordeaux-Cedex, F-33076, Fr.
SO Naunyn-Schmiedeberg's Archives of Pharmacology (1997), 356(2), 257-262
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer
DT Journal
LA English
AB The kinetics of transformation of CPT-11 to SN-38 by human liver microsomes from several donors were investigated in vitro. Microsomes from 7 livers were studied individually or as a pooled preparation CPT-11, either in its lactone or its carboxylate form, was added over a range of concns. The SN-38 formed was measured by HPLC with fluorometric

detection. In the deacylation-limited carboxylesterase reaction, the linear steady-state kinetics between 10 and 60 min were determined At all concns. of CPT-11 tested, the steady-state velocity of SN-38 formation as well as the intercept concns. of SN-38 were about 2-fold higher when the substrate was in the lactone form than in the carboxylate form. K'm and Vmax were estimated to be 23.3 μM and 1.43 pmol/min/mg, resp., for the lactone and 48.9 μM and 1.09 pmol/min/mg, resp., for the carboxylate form of CPT-11. It is concluded that the greater rate of conversion of CPT-11 lactone than of the carboxylate may contribute to the predominance of SN-38 lactone in plasma observed in vivo. The interindividual variation of SN-38 formation was relatively high (ratio of 4 between extreme values) but no large age- or gender-related differences were seen. The effect of 11 drugs of different therapeutic classes (antibiotics, antiemetics, antineoplastics, antidiarrheics, analgesics) which might be administered in association with irinotecan in the clin. setting, was evaluated in this system (total drug concentration: 100 μM; CPT-11 lactone concentration: 10 μM).

Loperamide and ciprofloxacin were the only drugs exerting a weak inhibition of CPT-11 conversion to SN-38.

L3 ANSWER 69 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:3606 CAPLUS
DN 126:114431
TI The cytotoxic activity of Bacillus anthracis lethal factor is inhibited by leukotriene A4 hydrolase and metallopeptidase inhibitors
AU Menard, Armelle; Papini, Emanuele; Mock, Michele; Montecucco, Cesare
CS Cent. Biomem. Dip. Sci. Biomed., Univ. Padova, Padua, Italy
SO Biochemical Journal (1996), 320(2), 687-691
CODEN: BIJOAK; ISSN: 0264-6021
PB Portland Press
DT Journal
LA English
AB The lethal factor of Bacillus anthracis is central to the pathogenesis of anthrax. Its mechanism of action is still unknown. Recently, on the basis of sequence similarities, the authors suggested that lethal factor might act similarly to leukotriene A4 hydrolase (LTA4), a bifunctional enzyme also endowed with a metallopeptidase activity. Here the authors show that some inhibitors of the LTA4 hydrolase and metallopeptidase activities of LTA4 hydrolase also affect the cytotoxicity of the anthrax lethal factor on macrophage cell lines, without interfering with the ability of the lethal factor to enter cells. These results support the proposal that anthrax lethal factor might display in the cytosol of intoxicated cells a peptidase activity similar to that of LTA4 hydrolase.

L3 ANSWER 70 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:674194 CAPLUS
DN 125:301599
TI Preparation and formulation of amino acid derivatives as LTA4 hydrolase inhibitors
IN Kawashima, Yoichi; Horiuchi, Masato
PA Santen Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

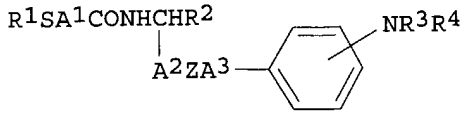
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9627585	A1	19960912	WO 1996-JP521	19960305
	W: CA, CN, FI, KR, NO, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	JP 08301840	A2	19961119	JP 1996-47031	19960305

09986629

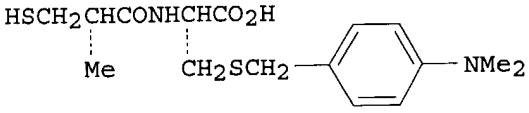
	JP 2909620	B2	19990623		
	EP 870762	A1	19981014	EP 1996-904324	19960305
	EP 870762	B1	20040428		
	R: CH, DE, FR, GB, IT, LI				
	US 5872281	A	19990216	US 1997-913093	19970905
PRAI	JP 1995-46816	A	19950307		
	WO 1996-JP521	W	19960305		

OS MARPAT 125:301599

GI



I



II

AB The title compds. I [R1 represents hydrogen, lower alkyl, Ph lower alkyl, lower alkanoyl or benzoyl, provided that the Ph ring in the Ph lower alkyl or benzoyl may be substituted by halogeno, lower alkyl or lower alkoxy; R2 represents carboxy optionally converted into ester, amide or hydroxamic acid; R3 represents lower alkyl; R4 represents lower alkyl; A1 represents lower alkylene optionally substituted by Ph, provided that the Ph group may be substituted by halogeno, lower alkyl or lower alkoxy; A2 represents lower alkylene; A3 represents lower alkylene; and Z represents S or O] are prepared The title compound II (preparation given) in vitro showed IC50 of 2.4 × 10-7 M against LTA4 hydrolase.

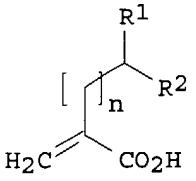
L3 ANSWER 71 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:642128 CAPLUS
DN 125:292619
TI Cardiorenal consequences of dual angiotensin converting enzyme and neutral endopeptidase 24.11 inhibition in transgenic rats with an extra renin gene
AU Wegner, Max; Hirth-Dietrich, Claudia; Knorr, Andreas; Dressel, Juergen; Ganten, Detlev; Stasch, Johannes-Peter
CS Cardiovascular and Arteriosclerosis Research, Bayer AG, Wuppertal, D-42096, Germany
SO Hypertension Research (1996), 19(3), 151-159
CODEN: HRESE4; ISSN: 0916-9636
PB Japanese Society of Hypertension
DT Journal
LA English
AB The cardiovascular consequences of mixed angiotensin converting enzyme and neutral endopeptidase (ACE/NEP) inhibition with alatriopril/alatrioprilat were compared with the consequences of endopeptidase (NEP) inhibition alone with (S)-thiorphan/ecadotril by determining the acute effects of the compds. on hemodynamic, hormonal, and renal parameters in hypertensive transgenic rats harboring an addnl. mouse renin gene (TGR(mRen2)27). Infusion of alatrioprilat and (S)-thiorphan in anesthetized TGR decreased blood pressure in a dose-dependent manner, but heart rate remained unchanged. The renal excretion of water, sodium, and cGMP also increased dose-dependently, with nearly the same maximal effects after infusion of (S)-thiorphan and alatrioprilat. At the end of infusion, plasma ANP and cGMP were elevated both after (S)-thiorphan and after alatrioprilat,

whereas plasma renin activity increased only after alatrioprilat. The ACE inhibition effect was studied in ganglion-blocked rats receiving a continuous infusion of angiotensin I. Alatrioprilat decreased the mean blood pressure dose-dependently, but about 30 times higher concns. were needed to produce the same effects as the ACE inhibitor captopril. At a dose of 30 mg/kg p.o., ecadotril, the orally active prodrug of (S)-thiorphan, decreased the systolic blood pressure in conscious TGR by 22 mmHg for 6 h, whereas alatriopril (100 mg/kg p.o.) also reduced the systolic pressure in these rats with a maximal reduction of 22 mmHg. In addition, ecadotril and alatriopril significantly increased the urinary excretion of sodium. In contrast, ACE inhibition with captopril decreased the excretion of sodium dose-dependently in conscious TGR. In conclusion, combined ACE/NEP inhibition produced a comparable lowering of blood pressure and improvement in renal function as those with NEP inhibition in TGR. Dual ACE/NEP inhibition may therefore be useful in cardiovascular conditions such as hypertension or heart failure.

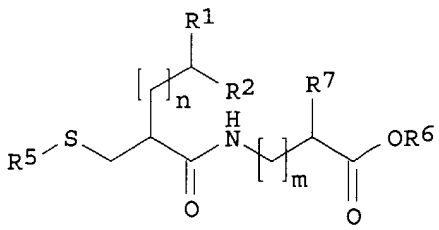
L3 ANSWER 72 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:628539 CAPLUS
DN 125:275420
TI Process for the synthesis of alpha-substituted acrylic acids, and their application as intermediates for amino acid derivatives
IN Duhamel, Pierre; Duhamel, Lucette; Danvy, Denis; Monteil, Thierry; Lecomte, Jeanne-Marie; Schwartz, Jean-Charles
PA Societe Civile Bioprojet, Fr.
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 729936	A1	19960904	EP 1996-400451	19960301
	EP 729936	B1	19990707		
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	FR 2731219	A1	19960906	FR 1995-2494	19950303
	FR 2731219	B1	19970425		
	CA 2170822	AA	19960904	CA 1996-2170822	19960301
	US 5786494	A	19980728	US 1996-609209	19960301
	AT 181910	E	19990715	AT 1996-400451	19960301
	ES 2136946	T3	19991201	ES 1996-400451	19960301
	JP 08325194	A2	19961210	JP 1996-73170	19960304
	US 5945548	A	19990831	US 1998-82866	19980521
PRAI	FR 1995-2494		19950303		
	US 1996-609209		19960301		

OS CASREACT 125:275420; MARPAT 125:275420
GI



I



II

AB Title acids I [R1, R2 = H, alkyl, cycloalkyl, (un)substituted Ph,

naphthyl, (un)substituted heterocyclo-fused Ph; n = 0-10] are prepared via corresponding alkylidenemalonate and alkylmalonate esters. Compds. I are useful as intermediates for N-(mercaptoacyl) amino acids II [R1, R2 = as above; R5 = H, acyl; R6 = H, alkyl, Ph, phenylalkyl; R7 = H, alkyl, Ph, (un)substituted alkyl; n, m = 0-10]. II are known inhibitors of neutral endopeptidase and angiotensin-converting enzyme, and are useful as antihypertensives, etc. (no data). For example, Knoevenagel condensation of PhCHO with CH2(CO2Et)2 in the presence of piperidine and AcOH, in refluxing PhMe with removal of H2O, gave PhCH:C(CO2Et)2. This was hydrogenated over Pd/C at 15 bar to give PhCH2CH(CO2Et)2, which was hydrolyzed with aqueous NaOH to give PhCH2CH(CO2H)2. The latter was heated with Et2NH and paraformaldehyde to give the objective acid CH2:C(CH2Ph)CO2H (III) in 78% yield for 4 steps. Addition reaction of AcSH with III (95%) and coupling with benzyl glycinate (as tosylate salt) using the DCC/HOBt method (90%) gave AcSCH2CH(CH2Ph)CONHCH2CO2CH2Ph.

L3 ANSWER 73 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:577729 CAPLUS
DN 125:222442
TI Preparation of N-(mercaptoalkanoyl)dipeptides and -amino acid derivatives with metallopeptidase inhibitory activity
IN Pellacini, Franco; Romagnano, Stefano; Norcini, Gabriele; Santangelo, Francesco
PA Zambon Group S.P.A., Italy
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9622998	A1	19960801	WO 1996-EP251	19960123
	W: AU, BY, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SI, SK, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2210151	AA	19960801	CA 1996-2210151	19960123
	AU 9646207	A1	19960814	AU 1996-46207	19960123
	EP 805817	A1	19971112	EP 1996-901752	19960123
	EP 805817	B1	20010816		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI				
	JP 10512870	T2	19981208	JP 1996-522617	19960123
	AT 204294	E	20010915	AT 1996-901752	19960123
	ES 2162022	T3	20011216	ES 1996-901752	19960123
	PT 805817	T	20020130	PT 1996-901752	19960123
	US 5866604	A	19990202	US 1996-750995	19961224
	US 5994539	A	19991130	US 1997-993567	19971218
PRAI	IT 1995-MI132	A	19950127		
	WO 1996-EP251	W	19960123		
	US 1996-774298	A3	19961224		

OS MARPAT 125:222442
AB Compds. of formula R(CH2)nCHR1CONH(CHR2CONH)mCH*(CH2R3)CO2R4 [R = HS, R5C(O)S convertible in the organism to SH group; wherein R5 = C1-4 alkyl, Ph; R1 = H, straight or branched C1-6 alkyl, aryl, aryl-C1-6 alkyl; R2 = H, straight or branched C1-6 alkyl, aryl-C1-6 alkyl; wherein aryl = (un)substituted Ph, biphenylyl, naphthyl, or 5- or 6-membered aromatic heterocyclyl; R3 = (un)substituted biphenylyl; R4 = H, C1-4 alkyl, CH2Ph; m, n = 0,1], which are endowed with both angiotensin converting enzyme-inhibitory and neutral endopeptidase enzyme-inhibitory activity and are useful in the treatment of cardiovascular diseases such as hypertension, renal failure, congestive heart failure, and ischemic cardiopathologies, are prepared Thus, a mixture of 2.5 g 3-benzoylthio-2-benzylpropionic acid, (1,1'-biphenyl-4-yl)-L-phenylalanine Me ester

hydrochloride, and 1.14 mL Et3N in THF and CH2Cl2 was successively treated with a solution of 1.1 g N-hydroxybenzotriazole in THF and a solution of 2.02 g DCC in CH2Cl2 at 0° with stirring and stirred for 20 h to give N-(3-benzoylthio-2-benzylpropionyl)-(1,1'-biphenyl-4-yl)-L-phenylalanine Me ester. The latter compound (1.84 g) was suspended in ethanol, degassed by bubbling N to eliminate O, treated dropwise an aqueous degassed solution of

9

mL 1 N NaOH at 5° and at the end of addition with degassed ethanol, stirred at room temperature for 4 h, cooled at 0°, and acidified with 5% aqueous HCl, to give N-(3-mercapto-2-benzylpropionyl)-(1,1'-biphenyl-4-yl)-L-phenylalanine. The latter compound and N-[(2S)-3-mercapto-2-benzylpropionyl]-(1,1'-biphenyl-4-yl)-L-phenylalanine showed IC50 of 5 and 2.6 nM, resp., against angiotensin converting enzyme (vs. 5, 99, and 3 nM for RB105, thiorphan, and captopril, resp.) and IC50 of 5 and 1.8 nM, resp., against neutral endopeptidase enzyme (vs. 24, 11 nM, and not active for RB105, thiorphan, and captopril, resp.).

L3 ANSWER 74 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:541331 CAPLUS
DN 125:185831
TI Renal and antihypertensive effects of neutral endopeptidase inhibition in transgenic rats with an extra renin gene
AU Stasch, Johannes-Peter; Hirth-Dietrich, Claudia; Ganten, Detlev; Wegner, Max
CS Cardiovascular Arteriosclerosis Res., Bayer AG, Wuppertal, Germany
SO American Journal of Hypertension (1996), 9(8), 795-802
CODEN: AJHYE6; ISSN: 0895-7061
PB Elsevier
DT Journal
LA English
AB The cardiovascular consequences of neutral endopeptidase (NEP) inhibition with the NEP inhibitor ecadotril were evaluated by determining acute and long-term effects of the compound on hemodynamic, hormonal, renal, and structural parameters in hypertensive transgenic rats harboring a mouse renin gene (TGR(m(Ren2)27)) and in normotensive controls (Sprague-Dawley rats, SDR). Acute administration of ecadotril (10 and 30 mg/kg, orally) produced a dose-dependent decrease in systolic blood pressure with a maximal effect of -23 mm Hg between 2 and 4 h after oral administration. The NEP activity in plasma was significantly inhibited and the plasma levels of atrial (ANP) and brain (BNP) natriuretic peptides and their second messenger, cyclic GMP, were distinctly raised after oral administration. In addition, ecadotril (10 and 30 mg/kg, orally) produced a dose-dependent increase in the urinary excretion of sodium and cyclic GMP. These effects were more pronounced in TGR(mRen2)27 than in the normotensive SDR without an activated natriuretic peptide system. In the long-term study, the systolic pressure in control TG (m(Ren2)27) rats increased from 213 ± t to 255 ± 7 mm Hg, whereas, in animals treated with ecadotril (30 mg/kg, orally twice daily), the blood pressure increased only from 213 ± 5 to 227 ± 6 mm Hg during the observation period of 13 wk. The increases in heart weight and in kidney weight were also delayed. At the end of the study, cyclic GMP was elevated and ANP tended to be higher, whereas plasma renin activity had decreased. These data indicate a beneficial pharmacol. profile of neutral endopeptidase inhibition that could prove useful in the treatment of cardiovascular diseases like hypertension.

L3 ANSWER 75 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:447437 CAPLUS
DN 125:104750
TI Role of neutral endopeptidase 24.11 in AV fistular rat model of heart failure
AU Wegner, M.; Hirth-Dietrich, C.; Stasch, J. -P.

09986629

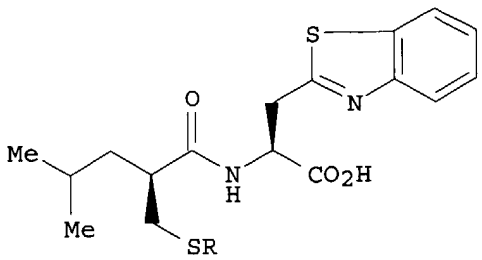
CS Cardiovascular and Arteriosclerosis Research, Bayer AG, Wuppertal, D-42096, Germany
SO Cardiovascular Research (1996), 31(6), 891-898
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier
DT Journal
LA English
AB The aortovenocaval fistular (AVF) rat represents a model of heart failure caused by increased cardiac volume overload and reduced renal function. Both circulating vasoconstrictors like the renin-angiotensin-aldosterone system and vasodilators like atrial and brain natriuretic peptides (ANP and BNP) are activated in this animal model of heart failure. In addition, neutral endopeptidase 24.11 (NEP) in plasma and urine is elevated in AVF rats. In the present investigation, the authors examined the renal and hormonal effects of the NEP inhibitor, ecadotril, in acute and chronic studies in rats with an aortovenocaval fistula (AVF). Sprague Dawley rats (350-430 g) were prepared by introducing a shunt between abdominal aorta and the vena cava. Acute administration of the neutral endopeptidase inhibitor, ecadotril (30 mg/kg p.o.), improved the reduced renal excretion of sodium in AVF rats (83 to 145 μmol/kg/h) but had no effect in sham-operated rats. However, neutral endopeptidase activity in urine was decreased after ecadotril in both groups. Plasma ANP was increased after ecadotril only in AVF rats (275 to 748 pg/mL), whereas the increase in plasma BNP was not statistically significant. After 4 wk of observation, the ANP and BNP plasma levels, renin activity (PRA), angiotensin I, and neutral endopeptidase activity were higher in AVF rats than in sham-operated rats. Four weeks on ecadotril (30 mg/kg p.o., b.i.d.) increased plasma ANP and decreased PRA in AVF rats. Plasma NEP activity was inhibited in both groups. Ventricle weight was higher in AVF rats than in sham-operated controls, and ecadotril treatment over 4 wk decreased ventricular hypertrophy to a slight extent. Thus, in the AVF rat model of heart failure, the neutral endopeptidase inhibitor ecadotril improves the reduced kidney function in AVF rats by raising natriuretic peptides in plasma and probably in urine. NEP inhibition with ecadotril could therefore offer useful therapeutic possibilities in the treatment of heart failure.

L3 ANSWER 76 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:323067 CAPLUS
DN 125:11459
TI Preparation of N-(mercaptoacyl)amino acid derivatives as inhibitors of neutral endopeptidase and angiotensin converting enzyme
IN Shiokawa, Yoichi; Takimoto, Koichi; Takenaka, Kohei; Kobayashi, Yuiko; Okitsu, Osamu
PA Fujisawa Pharmaceutical Co, Japan
SO Jpn. Kokai Tokkyo Koho, 23 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 08041015	A2	19960213	JP 1994-194775	19940727
PRAI	JP 1994-194775		19940727		

OS MARPAT 125:11459
GI

09986629



I

AB The title amino acid derivs. R3S(CH2)nCH(XR1)CONHCH(YR2)Z [R1 = lower alkyl, lower cycloalkyl, aryl, heterocyclyl; R2 = H, lower alkyl, heterocyclyl; R3 = H, HS-protecting group; X = S, lower alkylene, O, NH, NR4; R4 = lower alkyl; Y = lower alkylene; Z = (un)protected CO2H; n = 0,1], useful for treating and preventing hypertension, heart failure, angina pectoris, heart blood vessel disorders, kidney failure, cyclic edema, hyperaldosteronism, high urine calcium, glaucoma, asthma, pain, epilepsy, dementia, obesity, digestive tract diseases (diarrhea irritable bowel syndrome), and high blood renin, are prepared Thus, a solution of 1.03 g 2-acetylthiomethyl-4-methylpentanoic acid in 5 mL CH2Cl2 was treated with 0.7 mL SOCl2 and one drop of DMF , and stirred at room temperature for 3 h, and concentrated in vacuo to give 2-acetylthiomethyl-4-methylpentanoyl chloride. A suspension of 1.10 g (S)-3-(1,3-benzothiazol-2-yl)alanine (preparation given) in 10 mL MeCN was treated with N,O-bis(trimethylsilyl)acetamide under ice-cooling and stirred at room temperature for 3.5 h to give a reaction solution, which was treated with a solution of the above acid chloride in MeCN, stirred at room temperature for 4 h, and poured into 5% aqueous HCl to give, after workup and silica gel chromatog., 0.31 g (S,S)-diastereomer (I; R = Ac) and 0.09 g (R,S)-diastereomer. A solution of the (S,S)-diastereomer was treated with aqueous 28% NH3 and stirred at room temperature for 30 min to give the title compound I (R = H), which showed IC50 of 2.3 + 10-8 and 3.0 + 10-8 M against neutral endopeptidase and angiotensin converting enzyme, resp.

L3 ANSWER 77 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:1000100 CAPLUS
DN 124:21798
TI Ecadotril as a renal protective agent
IN Fujimura, Akio
PA Shionogi and Co., Ltd., Japan; Bayer Yakuhin, Ltd.
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9528921	A1	19951102	WO 1995-JP776	19950420
	W: AU, CA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	JP 07291863	A2	19951107	JP 1994-107872	19940421
	AU 9522670	A1	19951116	AU 1995-22670	19950420
PRAI	JP 1994-107872	A	19940421		
	WO 1995-JP776	W	19950420		

AB The object of the present invention is to produce a renal protective agent which protects kidneys from inducer of renal toxicity, thus, enabling repeated administration of the immunosuppressor for an extended period of time to prevent rejection after organ transplantation. Ecadotril shows

extremely potent renal protection activity, effectively suppresses renal toxicity of cyclosporin A.

L3 ANSWER 78 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:941609 CAPLUS
DN 124:21424
TI Neutral endopeptidase versus angiotensin converting enzyme inhibition in essential hypertension
AU Favrat, Bernard; Burnier, Michel; Nussberger, Jurg; Lecomte, Jeanne M.; Brouard, Remi; Waeber, Bernard; Brunner, Hans R.
CS Division Hypertension, Lausanne University, Lausanne, Switz.
SO Journal of Hypertension (1995), 13(7), 797-804
CODEN: JOHYD3; ISSN: 0263-6352
PB Current Science
DT Journal
LA English
AB Our objective was to evaluate the antihypertensive efficacy of sinorphan, an orally active inhibitor of neutral endopeptidase EC 3.4.24.11. The ability of sinorphan (100 mg twice a day) to lower blood pressure was compared with that of the angiotensin converting enzyme (ACE) inhibitor captopril (25 mg twice a day) using a randomized-sequence, double-blind crossover design in 16 patients with essential hypertension. Each treatment was administered for 4 wk and treatments were separated by a 3-wk placebo period. At the end of the last phase of treatment sinorphan was combined with captopril for a further 4-wk period. The changes in systolic (SBP) and diastolic blood pressure (DBP) were monitored using repeated ambulatory blood pressure monitoring. When given as monotherapy for 4 wk, neither sinorphan nor captopril significantly reduced the 24-h or the 14-h daytime mean SBP or DBP. However, a significant decrease in DBP was observed during the first 6 h after the morning administration of captopril. With sinorphan only a significant decrease in night-time SBP was found. With the combined therapy of sinorphan and captopril, significant decreases both in SBP and in DBP were observed, which were sustained over 24 h. After 4 wk of sinorphan alone or in combination with captopril, no change in plasma atrial natriuretic peptide level was found. However, urinary cyclic GMP excretion increased transiently after administration of the neutral endopeptidase inhibitor. Neutral endopeptidase inhibition with sinorphan has a limited effect on blood pressure in hypertensive patients when given alone. However, simultaneous neutral endopeptidase and ACE inhibition induces a synergistic effect, and might therefore represent an interesting new therapeutic approach to the treatment of essential hypertension.

L3 ANSWER 79 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:915309 CAPLUS
DN 124:87774
TI Kelatorphan and related analogs: potent and selective inhibitors of leukotriene A4 hydrolase
AU Penning, Thomas D.; Askonas, Leslie J.; Djuric, Stevan W.; Haack, Richard A.; Yu, Stella S.; Michener, Marshall L.; Krivi, Gwen G.; Pyla, E. Yvonne
CS Dep. Chem., Searle Res. and Development, Skokie, IL, 60077, USA
SO Bioorganic & Medicinal Chemistry Letters (1995), 5(21), 2517-22
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
OS CASREACT 124:87774
AB The hydroxamic acid-containing peptide kelatorphan, a known inhibitor of enkephalin-degrading enzymes, is a potent, non-competitive inhibitor of leukotriene A4 (LTA4) hydrolase. Analogs of kelatorphan were prepared and several sigvificantly and selectively inhibited both the hydrolase and aminopeptidase activity of the enzyme.

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L3 ANSWER 80 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:796278 CAPLUS
DN 124:30284
TI Diastereoselective synthesis of mixanpril, an orally active dual inhibitor of neutral endopeptidase and angiotensin converting enzyme
AU Turcaud, Serge; Gonzalez, Walter; Michel, Jean-Baptiste; Roques, Bernard P.; Fournie-Zaluski, Marie-Claude
CS Departement de Pharmacochimie Moleculaire et Structurale, U.F.R. des Sciences Pharmaceutiques et Biologiques, Paris, 75270, Fr.
SO Bioorganic & Medicinal Chemistry Letters (1995), 5(17), 1893-8
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
OS CASREACT 124:30284
AB A new diastereoselective synthesis of mixanpril, N-[(2S,3R)-2-benzoylthiomethyl-3-phenylbutanoyl]-L-alanine, a dual inhibitor of neutral endopeptidase and angiotensin converting enzyme, which could be used in the treatment of chronic hypertension and cardiac failure has been developed in order to obtain large quantities of this compound necessary for preclin. screening. A complete inhibition of both enzymes was obtained after oral administration of mixanpril in anesthetized rats.

L3 ANSWER 81 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:752958 CAPLUS
DN 123:253303
TI Prolonged inhibition of neutral endopeptidase 24.11 by sinorphan in stroke-prone spontaneously hypertensive rats
AU Stasch, Johannes-Peter; Knorr, Andreas; Wegner, Max; Hirth-Dietrich, Claudia
CS Cardiovascular and Arteriosclerosis Research, Bayer AG, Wuppertal, Germany
SO Hypertension Research (1995), 18(2), 137-43
CODEN: HRESE4; ISSN: 0916-9636
PB Japanese Society of Hypertension
DT Journal
LA English
AB The cardiovascular consequences of inhibition of the neutral endopeptidase 24.11 (NEP) with the orally active NEP inhibitor sinorphan were evaluated by determining long-ter effects of the drug on hemodynamic, hormonal and structural parameters in stroke-prone spontaneously hypertensive rats (SHR-SP). Systolic blood pressure increased in young SHR-SP from 194 ± 2 to 266 ± 7 mmHg, whereas in sinorphan (30 mg/kg orally bid) treated animals systolic blood pressure increased only from 193 ± 4 to 229 ± 4 mmHg during the treatment period of 9 wk. The increase in relative heart weight was also delayed. Plasma ANP was higher in the sinorphan group than in controls. The results of a second study demonstrate a substantial improvement of cardiac pump function and ventricular hypertrophy in old SHR-SP with compromised cardiac function by long-term inhibition of NEP. Thirteen-month-old SHR-SP were treated with sinorphan (30 mg/kg orally) for two weeks. At the end of experiment, the increase in ANP plasma levels did not reach statistical significance, whereas plasma cGMP was higher in sinorphan treated animals than in controls. Left ventricular end-diastolic pressure was markedly elevated in controls and significantly lower in sinorphan treated animals. In addition, sinorphan reduced cardiac hypertrophy in these old SHR-SP. In conclusion, the results of the present studies demonstrate that long-term NEP inhibition with sinorphan has inhibitory effects on malignant hypertensions and associated cardiac hypertrophy in young SHR-SP on a high-sodium diet. NEP inhibition substantially improves cardiac pump function and reduces ventricular hypertrophy of old SHR-SP with compromised cardiac function.

L3 ANSWER 82 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:733998 CAPLUS
DN 123:194953
TI Peripheral excitatory effects of two enkephalinase inhibitors, acetorphan and thiorphan, and an enkephalin analog, [D-Ala2-Met5]-enkephalinamide, on uterine motility in periparturient rats in vivo and in vitro
AU Adjroud, O.
CS Lab. Feto-Maternal Physiol., Univ. Rouen, Mont Saint Aignan, 76130, Fr.
SO Journal of Reproduction and Fertility (1995), 104(2), 181-6
CODEN: JRPFA4; ISSN: 0022-4251
PB Journals of Reproduction and Fertility Ltd.
DT Journal
LA English
AB The effects of two enkephalinase inhibitors, acetorphan and thiorphan, and the enkephalin analog [D-Ala2-Met5]-enkephalinamide (DAMEA), on spontaneous uterine contractions were studied at day 21 of pregnancy in rats following treatment in vivo or in vitro. Acetorphan (10 mg kg-1) and thiorphan (1 mg kg-1), immediately after their IV administration, increased the duration of spontaneous contractions 3.4- and 4.6-fold, resp., but did not modify the maximum amplitude. Similarly, thiorphan (40 μmol l-1) increased the duration of contractions when administered in vitro. Thiorphan was ineffective during the first 30 min when given into the cerebral ventricles (50 μg per rat). These results suggest that the enkephalinase inhibitors are acting via a peripheral opioid pathway; and this conclusion is supported by the observation that thiorphan potentiated the stimulatory effect of a submaximal dose of DAMEA administered in vitro. The excitatory effects of DAMEA and the enkephalinase inhibitors were blocked by naloxone. This antagonistic effect of naloxone on uterine motility in the periparturient rat uterus, induced by either acetorphan and thiorphan or DAMEA, seems to be regulated by peripheral opiate receptors. Naloxone (10 mg kg-1 s.c.) increased both the amplitude and duration of uterine motility in vivo; however, naloxone (26 μmol l-1 and 52 μmol l-1) produced a paradoxical dose-dependent biphasic effect in vitro.

L3 ANSWER 83 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:634496 CAPLUS
DN 123:56557
TI Preparation of N-thioacylated amino acids and peptides as antihypertensive agents
IN Fournie-Zaluski, Marie-Claude; Roques, Bernard-pierre
PA Institut National de la Sante et de la Recherche Medicale (INSERM), Fr.
SO PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9417036	A1	19940804	WO 1993-EP147	19930122
	W: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
	AU 9334940	A1	19940815	AU 1993-34940	19930122
	US 5591891	A	19970107	US 1994-185563	19940124
	US 5801274	A	19980901	US 1995-474980	19950607
PRAI	WO 1993-EP147		19930122		
	US 1994-185563		19940124		

OS MARPAT 123:56557
AB S-lipophilic aliphatic carbonyl [N-mercaptoacyl(amino acid or peptide)] compds. RSCH2CH(CHR1R2)CONHCHR3CO2R9, RSCH(CHA1R5)CONHCH(CHA2R5)CONR7CHR7C

O2R8 [R = lipophilic aliphatic carbonyl radical; R1 = aryl, heteroaryl; R2 = alkyl, or alkylene attached to the neighboring CH moiety and R1; R3 = H, alkyl, aryl, alkoxy, aryloxy; R4, R5 = H, alkyl, aryl, aralkyl, alkoxy, alkyloxymethyl, aralkyloxy; A1, A2 = H, alkyl, or together with CHR4 or CHR5, resp., form Ph, benzocycloalkyl; R6 = H, alkyl; R7 = cycloalkyl, aralkyl, aryloxymethyl, alkoxymethyl; R6R7 = atoms to form heterocyclyl; R8 = H, alkyl, aralkyl, cycloalkyl, alkyl, palmitoyl; R9 = H, alkyl, aralkyl, acyl, aroyl], were prepared Thus, 2-acetylthiomethyl-3-phenylbutanoic acid, tyrosine benzyl ester tosylate, Et3N, 1-hydroxybenzotriazole, and DCC were stirred in CHCl3/THF at 0-20° to give 80% N-(2-acetylthiomethyl-1-oxo-3-phenylbutyl)tyrosine benzyl ester. The latter inhibited neutral endopeptidase and angiotensin converting enzyme with IC50 = 5 nM and 4 nM, resp.

L3 ANSWER 84 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:394505 CAPLUS
DN 122:178247
TI Synthesis and pharmacological properties of 2-[S-acetylthiorphan]-1,3-diacylaminopropan-2-ol derivatives as chimeric lipid drug carriers containing an enkephalinase inhibitor
AU Lambert, Didier M.; Mergen, Frank; Berens, Catherine F.; Poupaet, Jacques H.; Dumont, Pierre
CS Sch. Pharm., Univ. Louvain, Brussels, B-1200, Belg.
SO Pharmaceutical Research (1995), 12(2), 187-91
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum
DT Journal
LA English
AB The design of 1,3-diacylaminopropan-2-ols as CNS-directed carrier groups is based on their resemblance to endogenous lipids and the properties of pseudotriglyceride esters to facilitate the brain penetration of therapeutic agents. 2-[S-acetylthiorphan]-1,3-diacylaminopropan-2-ols, differing from the nature of 1,3-acyl chains, were synthesized and evaluated in vivo using the hot-plate jump test. The compds. exhibited naloxone reversible analgesic properties. The effects were superior to those of parent compds. thiorphan and S-acetylthiorphan. The palmitoyl derivative showed also activity at 0.8 mmol/kg after oral administration. Like acetorphan, a thiorphan prodrug, these compds. were poor substrates for brain enkephalinase, suggesting the release of the pharmacol. active inhibitor at the site of action in the brain.

L3 ANSWER 85 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:234794 CAPLUS
DN 122:23858
TI Treatment of osteoporosis with opioids, opioid-degrading enzyme inhibitors, enkephalin secretagogues, and mixtures thereof
IN D' Souza, Sharyn Mary; Ibbotson, Kenneth John
PA Procter and Gamble Co., USA
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9421242	A1	19940929	WO 1994-US2304	19940302
	W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, UA, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9462530	A1	19941011	AU 1994-62530	19940302
PRAI	US 1993-34930		19930319		

09986629

WO 1994-US2304 19940302
OS MARPAT 122:23858
AB Osteoporosis is treated in a human or other animal subject by administering a safe and effective amount of an active agent selected from the group consisting of opioids, opioid-degrading enzyme inhibitors, enkephalin secretagogues, and mixts. thereof. Thiorphan inhibited substrate degradation by enkephalinase and stimulated proliferation of osteoblast-like cells. A human female subject suffering from postmenopausal osteoporosis was treated for 2 yr with thiorphan in a cyclical regimen where each cycle consisted of an active period of 28 days with thiorphan administration followed by a nonactive period of 28 days with administration of a daily supplement of calcium. A tablet and an i.v. injection formulation are given.

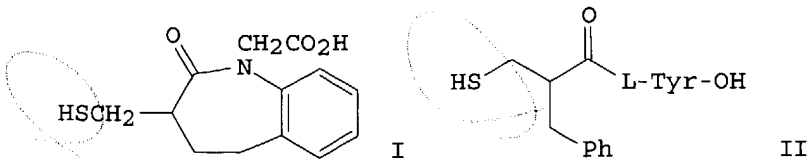
L3 ANSWER 86 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:595603 CAPLUS
DN 121:195603
TI Locomotor and analgesic effects of morphine and acetorphan in rats chronically treated with morphine or thiorphan
AU Khallouk-Bousselmame, R.; Costentin, J.
CS Unite de Neuropsychopharmacologie Experimentale, U.R.A. 1170 du C.N.R.S., European Institute for Peptide Research, Faculte de Medecine and Pharmacie de Rouen, 76803, Saint-Etienne du Rouvray, Fr.
SO European Neuropsychopharmacology (1994), 4(2), 137-43
CODEN: EURNE8; ISSN: 0924-977X
DT Journal
LA English
AB A continuous 8-day s.c. administration of morphine (450 μg/kg/h) sensitized rats to the morphine-induced stimulation of locomotion (morphine test dose = 3 mg/kg, s.c.) but not to the acetorphan (5 mg/kg, i.v.)-induced stimulation of locomotion. On the other hand, a continuous 10-day intracerebroventricular infusion of the enkephalinase inhibitor, thiorphan (25 μg/rat/h), known to desensitize the acetorphan-induced stimulation of locomotion, also desensitized the morphine (3 mg/kg, s.c.)-induced stimulation of locomotion. The continuous 10-day, s.c. administration of morphine desensitized to the morphine (3 mg/kg, s.c.)- but not acetorphan (5 mg/kg, i.v.)-induced analgesia, as measured by the latency to jump from a hot plate (55°C). On the other hand, the continuous 10-day intracerebroventricular infusion of thiorphan did not desensitize to morphine (3 mg/kg, s.c.)-induced analgesia. Thus, the chronic actions of morphine and thiorphan, according to the tested function, did not result in cross-sensitization (locomotion) or cross-tolerance (nociception). These differences could depend on the involvement of different opioid receptors (mu vs. delta) and/or on different functional organizations.

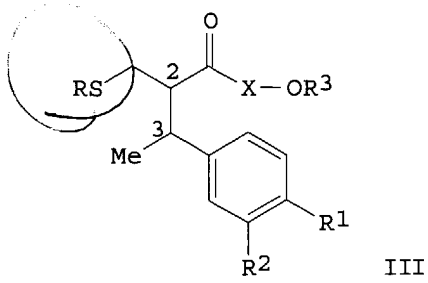
L3 ANSWER 87 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:549037 CAPLUS
DN 121:149037
TI Acute renal effects of neutral endopeptidase inhibition in humans
AU Schmitt, Francois; Martinez, Frank; Ikeni, Achour; Savoiu, Corneliu; Natov, Svetlozar; Laborde, Kathleen; Lacour, Bernard; Grunfeld, Jean-Pierre; Hannedouche, Thierry
CS Hopital Necker, Paris, 75743, Fr.
SO American Journal of Physiology (1994), 267(1, Pt. 2), F20-F27
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
AB The acute renal effects of neutral endopeptidase 24.11 (E-24.11) inhibition induced by a single oral dose of sinorphan (100 mg) were investigated in 10 healthy normotensive subjects on normal sodium diet. Sinorphan inhibited 90% of E-24.11 activity and increased plasma atrial

natriuretic peptide (ANP) and urinary guanosine 3',5'-cyclic monophosphate (cGMP) by 70 and 100%, resp. Sinorphan increased urinary sodium output by 50% (P <0.001) and decreased fractional distal reabsorption by 4% (P <0.01). Sinorphan increased glomerular filtration rate (GFR) and filtration fraction by 10% 1 h after administration and decreased renal plasma flow by 10%. Mean arterial pressure, renal vascular resistance, plasma aldosterone concentration, and renin activity were unmodified. Sinorphan decreased fractional clearance of neutral dextrans over the 34- to 52-Å radius range. Applying the changes along with a hydrodynamic isopore with shunt model, sinorphan significantly increased capillary pressure gradient (ΔP; 39 ± 1 vs. 34 ± 1 mmHg; P <0.01), whereas ultrafiltration coefficient was unchanged. In conclusion, endopeptidase inhibition increased endogenous plasma ANP and cGMP generation and induced natriuresis through both an increase in filtered load and a decrease in distal tubular reabsorption of sodium. Sinorphan increases GFR, filtration fraction, and ΔP, probably through an increase in efferent over afferent arteriolar resistance ratio.

L3 ANSWER 88 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:499078 CAPLUS
DN 121:99078
TI Mercaptoacyl amino acid inhibitors of atriopeptidase. 1. Structure-activity relationship studies of methionine and S-alkylcysteine derivatives
AU Neustadt, Bernard R.; Smith, Elizabeth M.; Nechuta, Terry L.; Bronnenkant, Alan A.; Haslanger, Martin F.; Watkins, Robert W.; Foster, Caroline J.; Sybertz, Edmund J.
CS Schering-Plough Research Institute, Kenilworth, NJ, 07033-0539, USA
SO Journal of Medicinal Chemistry (1994), 37(15), 2461-76
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
AB A broad series of N-(3-mercaptoacyl) amino acid derivs. was evaluated for their ability to inhibit atriopeptidase (neutral endopeptidase, EC 3.4.24.11) in vitro and in vivo. Structural parameters studied were (i) the substituent on the 2-position of the 3-mercaptopropionyl moiety, (ii) the amino acid component, (iii) the S-terminal derivative, and (i.v.) the C-terminal derivative Optimum activity was observed for derivs. of methionine and S-alkylcysteines. N-[3-Mercapto-2(S)-[(2-methylphenyl)methyl]-1-oxopropyl]-L-methionine was identified as a highly effective inhibitor of atriopeptidase meriting evaluation as a potential cardiovascular therapeutic agent.

L3 ANSWER 89 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:436156 CAPLUS
DN 121:36156
TI New Dual Inhibitors of Neutral Endopeptidase and Angiotensin-Converting Enzyme: Rational Design, Bioavailability, and Pharmacological Responses in Experimental Hypertension
AU Fournie-Zaluski, Marie-Claude; Coric, Pascale; Turcaud, Serge; Rousselet, Nathalie; Gonzalez, Walter; Barbe, Brigitte; Pham, Isabelle; Jullian, Nathalie; Michel, Jean-Baptiste; Roques, Bernard P.
CS Unite de Pharmacochimie Moleculaire et Structurale, UFR des Sciences Pharmaceutiques et Biologiques, Paris, 75270, Fr.
SO Journal of Medicinal Chemistry (1994), 37(8), 1070-83
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI





AB Dual inhibitors were designed by a rational approach based on the characteristics of the active sites of both angiotensin-converting enzyme (ACE) and epithelial neutral endopeptidase (NEP), enzymes which belong to the same family of zinc metallopeptidases, and on the structures of their most potent and selective inhibitors. As both NEP and ACE contain a large S'1-S'2 domain able to accommodate aromatic residues, the cyclic ACE inhibitor I was selected as a template. Various aliphatic constraints were introduced on the benzyl moiety of the potent NEP inhibitor II to improve the fit between the computed most stable conformers of these mols. and the ACE template. New dual inhibitors, of general formula III [R = H, Ac, Bz, adamantylcarbonyl; R1 = H, F, OMe, NH2, OH, R2 = H, F, OMe, R1R2 = OCH2O, X = Gly, Ala, Val, Leu, Nle, L-2-aminobutanoic acid, Tyr, Ser(CH2Ph), Nva, Tyr(Ac), R3 = H, CH2Ph] with IC50 values in the nanomolar range for both enzymes were generated by this approach. The separation of the four stereoisomers using chiral amines and the stereoselective synthesis of the 2-(mercaptomethyl)-3-phenylbutanoyl moiety showed that inhibitors 2S,3R-III are the most potent on both NEP and ACE. The "in vivo" potency of various prodrugs of these inhibitors to inhibit ACE activity in lung and NEP activity in kidney was measured after oral administration in mice. From this pharmacokinetic study the most potent dual inhibitor (2S,3R)-III (R-R3 = H, X = Ala) (RB 105) and its most efficient in vivo prodrug (2S,3R)-III (R = Bz, R1-R3 = H, X = Ala) (mixanpril) were selected. Competition expts. with a tritiated inhibitor of ACE or NEP bound to mouse lung and kidney membranes resp. showed that mixanpril has a long duration of action (>8 h). As expected, after i.v. administration in the spontaneously hypertensive rat (SHR), RB 105 decreased blood pressure and increased diuresis and natriuresis. Both effects were also observed after chronic oral administration of 50 mg/kg mixanpril twice a day in SHR. These results indicate that an efficient and orally active dual inhibitor of NEP and ACE produces beneficial changes in thermodn. and could represent a therapeutic progress in the treatment of cardiovascular diseases.

L3 ANSWER 90 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:331099 CAPLUS
DN 120:331099
TI N-(mercaptoacyl)peptidyl derivatives as antidegenerative agents
IN Hagmann, William K.; Kopka, Ihor E.
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent

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LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9407481	A1	19940414	WO 1993-US9137	19930927
	W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9352921	A1	19940426	AU 1993-52921	19930927
	US 5629343	A	19970513	US 1995-392730	19950223
PRAI	US 1992-957926	A2	19921002		
	WO 1993-US9137	W	19930927		

OS MARPAT 120:331099
AB Novel N-(mercaptoacyl)peptidyl compds. are useful as inhibitors of matrix metalloendoproteinases which degrade major components of articular cartilage and basement membranes causing degenerative diseases such as arthritis, periodontal disease, corneal ulceration, and certain cancers, are described. For example, N-(2-thiomethyl-4-phenylbutanoyl)-L-leucinamide was prepared and its inhibitory activity against stromelysin was tested in vitro.

L3 ANSWER 91 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:244372 CAPLUS
DN 120:244372
TI Preparation of N-substituted mercaptophenylpropanamide derivatives
IN Mimura, Tetsutaro; Nakamura, Yasuhisa; Nishino, Junko; Sawayama, Tadahiro; Sasagawa, Takashi; Deguchi, Takashi; Nakamura, Hideo
PA Dainippon Pharmaceutical Co., Ltd., Japan
SO U.S., 35 pp. Cont.-in-part of U.S. Ser. No. 503,969, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5210266	A	19930511	US 1990-609450	19901105
	US 5179125	A	19930112	US 1990-504654	19900404
PRAI	JP 1987-306763		19871203		
	JP 1988-200697		19880810		
	US 1988-274843		19881122		
	US 1990-503969		19900404		
	US 1990-504654		19900404		

OS MARPAT 120:244372
AB Title compds. R1CHWCH(R2CH2)CONHXR3 (R1 = mercapto, group convertible into mercapto; W = H, alkyl, aralkyl; R2 = (substituted) aryl, heterocyclyl, alkyli, X = cycloalkylene, cycloalkylidene, phenylene which may have substituents or may be fused with a ring; R3 = carboxy, group convertible to carboxy) or a salt thereof having excellent enkephalinase inhibitory activity, useful as analgesics, are prepared 3-Amino-5-methylbenzoic acid, Et3N and 2-acetylthiomethyl-3-phenylpropionyl chloride in THF were stirred at room temperature for 2 h to give 3-[(2-acetylthiomethyl-3-phenylpropionyl)amino]-5-methylbenzoic acid which was treated with IN aqueous NaOH to give 3-[(2-mercaptomethyl-3-phenylpropionyl)amino]-5-methylbenzoic acid (I). I showed an oval ED50 of 20.2 mg/kg in a potentiation of analgesic activity of D-ala2-Met5-enkephalin in mice.

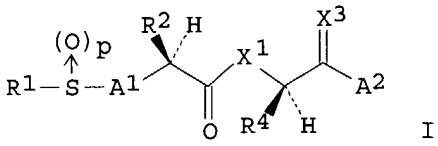
L3 ANSWER 92 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:31235 CAPLUS
DN 120:31235
TI Preparation of dipeptides as endothelin antagonists
IN Ishikawa, Kyobumi; Nagase, Toshio; Mase, Toshiaki; Niiyama, Kenji; Ihara,

09986629

Masaki; Yano, Mitsuo
PA Banyu Pharma Co Ltd, Japan
SO Jpn. Kokai Tokkyo Koho, 28 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 05178890	A2	19930720	JP 1991-361569	19911226
PRAI JP 1991-361569		19911226		

OS MARPAT 120:31235
GI



I

AB Title compds. [I; R1 = alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, etc.; R2 = alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, etc.; R4 = heterocyclylalkyl, etc.; X1 = O, (un)substituted imino; X3 = O, S; A1 = bond, (alkyl)alkylene; A2 = (un)substituted oxymethylamino, amino acid residue, etc.; p = 0-2 integer], endothelin antagonists and therefore useful for treating many ailments, are prepared and tested for their inhibiting activity against endothelin. E.g., I [R1 = cyclohexyl, R2 = Me2CHCH2, R4 = 1H-indan-3-ylmethyl, p = 1, A1 = bond, A2 = D-Trp-OMe, X1 = NH, X3 = O], prepared from the appropriate amino acid derivs., showed 66% inhibition against endothelin by binding with ET4 receptors in the smooth muscles from pig arteries.

L3 ANSWER 93 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:23408 CAPLUS
DN 120:23408
TI Analgesic potency of S-acetylthiorphan after intravenous administration to mice
AU Lambert, Didier M.; Mergen, Frank; Poupaert, Jacques H.; Dumont, Pierre
CS Sch. Pharm., Cathol. Univ. Louvain, Brussels, B-1200, Belg.
SO European Journal of Pharmacology (1993), 243(2), 129-34
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB As hydrolysis in serum of acetorphan to S-acetylthiorphan has been evidenced, both the neutral endopeptidase inhibition in vitro by acetylthiorphan and the analgesic potency of acetylthiorphan after i.v. administration to mice in 2 analgesic models, the hot-plate and the tail-flick tests, were compared with those of thiorphan and acetorphan. Acetylthiorphan caused less inhibition of neutral endopeptidase than did thiorphan. After i.v. administration followed by the hot-plate jump latency test, acetylthiorphan elicited a degree of analgesia equivalent to that from acetorphan but longer lasting. Like acetorphan and thiorphan, acetylthiorphan was devoid of analgesic activity in the tail-flick test. The results indicated that S-acetylation of the thiol function in acetylthiorphan ensures sufficient lipophilicity to permit crossing of the blood-brain barrier and that acetylthiorphan acts via a prodrug mechanism.

L3 ANSWER 94 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:626418 CAPLUS

09986629

DN 119:226418
TI Preparation of mercaptoacyl amino acids as inhibitors of neutral endopeptidase and peptidyldipeptidase A
IN Fournie-Zaluski, Marie Claude; Roques, Bernard Pierre
PA Institut National de la Sante et de la Recherche Medicale (INSERM), Fr.; Rhone-Poulenc Rorer SA
SO Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 539848	A1	19930505	EP 1992-117955	19921021
	R: PT				
	FR 2682952	A1	19930430	FR 1991-13174	19911025
	FR 2682952	B1	19931203		
	WO 9308162	A1	19930429	WO 1992-EP2412	19921021
	W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
	AU 9227895	A1	19930521	AU 1992-27895	19921021
	AU 666141	B2	19960201		
	EP 609310	A1	19940810	EP 1992-921688	19921021
	EP 609310	B1	19980729		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
	JP 07509441	T2	19951019	JP 1993-507446	19921021
	JP 3250806	B2	20020128		
	AT 168995	E	19980815	AT 1992-921688	19921021
	ES 2118833	T3	19981001	ES 1992-921688	19921021
	JP 2002030066	A2	20020129	JP 2001-155490	19921021
PRAI	FR 1991-13174	A	19911025		
	JP 1993-507446	A3	19921021		
	WO 1992-EP2412	A	19921021		

OS MARPAT 119:226418
AB RSCH2CH(CHR1R2)CONHCHR3CO2R4 [R = H, acyl, aroyl, cycloalkylcarbonyl, SCH2CH(CHR1R2)CONHCHR3CO2R4; R1 = alkyl; R2 = (hetero)aryl; R1 taken with an ortho carbon of R2 forms an alkylene chain; R3 = H, alkyl, aryl, alkoxy, aryloxy; R4 = H, alkyl, aralkyl, acyl, aroyl], were prepared Thus, 2-acetylthiomethyl-3-phenylbutanoic acid (preparation given), (S)-tyrosine benzyl ester tosylate, 1-hydroxybenzotriazole, Et3N, and DCC were stirred in THF/CHCl3 at 0-20° overnight to give 80% N-(2-acetylthiomethyl-1-oxo-3-phenylbutyl)tyrosine benzyl ester. This inhibited neutral endopeptidase and peptidyldipeptidase A with IC50's of 2.5 + 10-9 M and 1.8 + 10-9 M, resp.

L3 ANSWER 95 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:546591 CAPLUS
DN 119:146591
TI Pharmaceutical compositions containing atriopeptidase inhibitors and calcium antagonists
IN Lecomte, Jeanne Marie; Schwartz, Jean Charles
PA Societe Civile Bioprojet, Fr.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9311797	A1	19930624	WO 1992-FR1162	19921209

W: CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

	FR 2684553	A1	19930611	FR 1991-15290	19911210
	FR 2684553	B1	19950407		
	JP 06507180	T2	19940811	JP 1992-510661	19921209
PRAI	FR 1991-15290		19911210		
	WO 1992-FR1162		19921209		

AB Pharmaceutical compns. containing an atriopeptidase inhibitor, e.g. sinorphan (I) and a Ca antagonist, nifedipine (II) are used for the treatment of arterial hypertension, renal and chronic cardiac insufficiency. Rats whose left kidney was removed were implanted with 50 mg desoxycorticosterone acetate with free access to food and 9 g NaCl/L in water. Thus, administration of 10mg I/kg combined with 0.4 mg II/kg orally decreased the mean arterial pressure by 32-40 as compared to 25-30 mm Hg for 0.4mg II/kg. A tablet contained I 50, and II 100 mg.

L3 ANSWER 96 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:517815 CAPLUS
DN 119:117815
TI Importance of the amide bond of thiorphan in the inhibitor-enkephalinase docking process demonstrated with some thiorphan isosteres
AU Thierry, Monteil; Mitsuharu, Kotera; Lucett, Duhamel; Pierre, Duhamel; Claude, Gros; Nadine, Noel; Charles, Schwartz Jean; Marie, Lecomte Jeanne
CS URA 464, CNRS, Mont Saint Aignan, 76134, Fr.
SO Bioorganic & Medicinal Chemistry Letters (1992), 2(9), 949-54
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB The synthesis and enkephalinase-inhibiting activities of thiorphan amide bond isosteres HSCH2CH(CH2Ph)ZCH2CO2H (Z = COCH2, CH2NH, CSNH, E-CH:CH) are reported. A double chelation mechanism for the inhibitor-enkephalinase docking process is proposed.

L3 ANSWER 97 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:486708 CAPLUS
DN 119:86708
TI Action of enkephalinase (EC 3.4.24.11) inhibition on the pre- and post-prandial electromyographic patterns of colon in rats
AU Benouali, S.; Berard, H.; Roche, M.
CS Univ. Savoie, Chambery, 73011, Fr.
SO Neuropeptides (Edinburgh, United Kingdom) (1993), 24(5), 299-305
CODEN: NRPPDD; ISSN: 0143-4179
DT Journal
LA English
AB Endogenous opioids are an important regulatory factor for the digestive tract and specially for its motility pattern. Enkephalin degradation includes an enkephalinase (EC 3.4.24.11) and the effects on the colic electromyog. profile of its inhibition by acetorphan were investigated in the unrestrained rat. The electromyogram consisted of Long Spike Bursts (LSB). In fasted state, they propagated indifferently in both aboral and oral directions from any point of the colon. Feeding privileges LSB which start near the cecal junction and propagate aborally to the distal colon. The acetorphan treatment increases the percentage of LSB propagating aborally on the entire colon in fasted state and reinforces the increased percentage of LSB which propagated down on the entire colon induced by feeding. All the actions of acetorphan on the colic motility pattern disappear after inhibition of opioid receptors by naloxone. That may account for involvement of enkephalins in acetorphan properties on the pattern of the colic elec. activity.

L3 ANSWER 98 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:440268 CAPLUS

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DN 119:40268
TI 1,3-diacylaminopropan-2-ols and corresponding 2-acyl derivatives as drug carriers: Unexpected pharmacological properties
AU Lambert, D. M.; Neuvens, L.; Mergen, F.; Gallez, B.; Poupaert, J. H.; Ghysel-Burton, J.; Maloteaux, J. M.; Dumont, P.
CS Sch. Pharm., Cathol. Univ. Louvain, Brussels, B-1200, Belg.
SO Journal of Pharmacy and Pharmacology (1993), 45(3), 186-91
CODEN: JPPMAB; ISSN: 0022-3573
DT Journal
LA English
AB The design of lipid vectors (pseudotriglycerides, PTGs) achieved by the amide isosteric substitution of the ester moieties of 1,3-diacylglycerols, is based on the structural similarity with natural triglycerides facilitating the passage of pharmacol. agents across biol. membranes. 2-S-acetylthiorphan (hemiacetorphan) pseudotriglycerides, Z-glycine pseudotriglycerides and 1,3-diacylaminopropan-2-ols vector mols. differing by the nature of the acid side-chain are examined in acute toxicity, radioligand binding and guinea-pig ileum expts. These evaluations have led us to distinguish two types of compds. Linear derivs., palmitoyl and decanoyl, are devoid of toxicity and intrinsic activity. Cyclic derivs., which contain in the acyl chain a Ph, cyclohexyl, cyclopentyl or adamantoyl ring, present addnl. properties. Cyclic derivs. of hemiacetorphan are lethal after i.v. administration. The mortality is governed by the 2-hemiacetorphan moiety in the cyclic vector mols. Hemiacetorphan alone is also lethal. Cyclic vector mols. and related compds. inhibit the contractile response of the guinea-pig ileum induced by elec. stimulation, histamine or acetylcholine (noncompetitive antagonism) whereas linear entities and parent compds. are not active. In particular, the 2-hemiacetorphan 1,3-diadamantoylamide PTG presents pD'2 values 7.87 ± 0.29 (vs histamine) and 7.97 ± 0.12 (vs acetylcholine).

L3 ANSWER 99 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:16317 CAPLUS
DN 118:16317
TI Pharmaceutical compositions, particularly for the treatment of functional colopathy
IN Schwartz, Jean Charles; Lecomte, Jeanne Marie
PA Societe Civile Bioproject, Fr.
SO Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 501870	A1	19920902	EP 1992-400480	19920225
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
	FR 2673105	A1	19920828	FR 1991-2254	19910226
	FR 2673105	B1	19950113		
	JP 05105627	A2	19930427	JP 1992-75283	19920226
PRAI	FR 1991-2254		19910226		

AB (R)- Or (S)-acetorphan and mixts. of these are prepared and used for the treatment of intestinal disorders. The compds. were prepared by the reaction of 2-acetylthiomethyl-3-phenylpropanoyl chloride with benzyl glycinate. The effectiveness of compds. (at 10-100 mg) in treatment of functional colopathy in humans and laboratory animals was demonstrated.

L3 ANSWER 100 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:605015 CAPLUS
DN 117:205015
TI The effects of orally active enkephalinase inhibitors on morphine

withdrawal syndrome
AU Dzoljic, Mihailo; Bokszanska, Agness; Korenhof, Annemiek M.; Kaplan, Charles D.; Dzoljic, Misa; Rupreht, Jose; Zijlstra, Freek J.; Brinkman, Edwin C. A.; Cappendijk, Susan L. T.
CS Fac. Med. Health Sci., Erasmus Univ. Rotterdam, Rotterdam, 3000 DR, Neth.
SO NeuroReport (1992), 3(7), 637-40
CODEN: NERPEZ; ISSN: 0959-4965
DT Journal
LA English
AB Considerable evidence has accumulated to suggest that intracerebroventricular administration of enkephalinase inhibitors, which do not penetrate the blood-brain barrier, significantly attenuates the opioid withdrawal syndrome. Therefore, the aim of this study was to examine the effect of i.p. administration of orally active enkephalinase inhibitors, acetorphan (2,5-20 mg kg-1) and SCH34826 (15-120 mg kg-1). These drugs significantly decreased the severity of the naloxone precipitated withdrawal syndrome in morphine dependent rats and mice. It therefore appears that these orally active enkephalinase inhibitors are promising tools in studying modulation of opioid dependence phenomena.

L3 ANSWER 101 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:524284 CAPLUS
DN 117:124284
TI Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhea
AU Baumer, P.; Dorval, E. Danquechin; Bertrand, J.; Vetel, J. M.; Schwartz, J. C.; Lecomte, J. M.
CS Lab. Bioprojet Marnes la Coquette, Fr.
SO Gut (1992), 33(6), 753-8
CODEN: GUTTAK; ISSN: 0017-5749
DT Journal
LA English
AB Acetorphan is an orally active inhibitor of enkephalinase (EC 3.4.24.11) with antidiarrheal activity in rodents apparently through protection of endogenous enkephalins and a purely antisecretory mechanism. Its antidiarrheal activity in man was assessed in an exptl. model of cathartic-induced secretory diarrhea as well as in acute diarrhea of presumed infectious origin. In six healthy volunteers receiving castor oil and pretreated with acetorphan or placebo in a crossover controlled trial, the drug significantly decreased the number and weight of stools passed during 24 h. About 200 outpatients with severe acute diarrhea (more than five stools per day) were included in a randomized double blind study of acetorphan against placebo. The significant antidiarrheal activity of acetorphan was estimated using a variety of criteria: (i) the duration of both diarrhea and treatment were diminished; (ii) no acetorphan treated patient withdrew from the study whereas five dropped out because of worsening in the placebo group; (iii) the frequency of symptoms associated with diarrhea - for example, abdominal pain or distension, nausea and anorexia - remaining after two weeks was nearly halved; (i.v.) using visual analog scales acetorphan treatment was found more effective than placebo by both investigators and patients. There was statistically no significant difference between acetorphan and placebo with respect to side effects, particularly constipation, which often accompanies the antidiarrheal activity of mu opioid receptor agonists. This difference is attributable to the lack of antipropulsive activity of acetorphan in man. The efficacy and tolerance of acetorphan suggest that enkephalinase inhibition may represent a novel therapeutic approach for the symptomatic management of acute secretory diarrhea without impairing intestinal transit.

L3 ANSWER 102 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:503982 CAPLUS
DN 117:103982

09986629

TI Effects of acetorphan, an antidiarrheal enkephalinase inhibitor, on oro-caecal and colonic transit times in healthy volunteers
AU Bergmann, J. F.; Chaussade, S.; Couturier, D.; Baumer, P.; Schwartz, J. C.; Lecomte, J. M.
CS Clin. Ther., Hop. Lariboisiere, Fr.
SO Alimentary Pharmacology and Therapeutics (1992), 6(3), 305-13
CODEN: APTHEN; ISSN: 0269-2813
DT Journal
LA English
AB Acetorphan is a potent enkephalinase inhibitor displaying antidiarrheal activity attributable to its intestinal antisecretory action mediated by endogenous enkephalins. The effect of acetorphan on digestive motility was studied in 12 healthy volunteers. Oro-cecal transit time was evaluated using the sulfasalazine/sulfapyridine method and colonic transit times using radiopaque markers. These measurements were successively performed after one week treatment with an antidiarrheal dose of acetorphan (100 mg t.d.s.) or placebo. There was no significant modification in transit time linked to acetorphan treatment:total oro-cecal times were 303 min vs. 287 min and colonic transit times 25.8 h vs. 31.3 h after acetophan and placebo, resp. There was no significant modification either in right colonic, left colonic or rectosigmoid segmental transit times, or in the mean number of stools. These results, consistent with those from animal studies, confirm that, unlike classical antidiarrheal mu opiate receptor agonists, which act by delaying intestinal transit, acetorphan does not affect the transit. Antidiarrheal activity not accompanied by a delayed intestinal transit could have beneficial therapeutic consequences in the management of infectious diarrhea. In addition, the authors show that the sulfasalazine and radiopaque markers methods can be simultaneously applied in the same study.

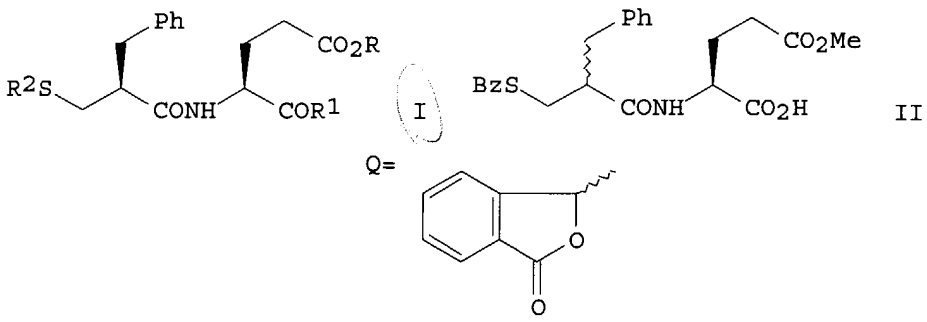
L3 ANSWER 103 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:470087 CAPLUS
DN 117:70087
TI Mixed-inhibitor-prodrug as a new approach toward systemically active inhibitors of enkephalin-degrading enzymes
AU Fournie-Zaluski, Marie Claude; Coric, Pascal; Turcaud, Serge; Lucas, Evelyne; Noble, Florence; Maldonado, Raphael; Roques, Bernard P.
CS Dep. Chim. Org., Univ. Rene Descartes, Paris, 75270, Fr.
SO Journal of Medicinal Chemistry (1992), 35(13), 2473-81
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
AB In order to evaluate the possible advantages of potentiating the effects of the endogenous enkephalins, to obtain analgesia without the serious drawbacks of morphine, it was essential to design systemically active compds. which inhibit the two metabolizing enzymes, aminopeptidase N (APN) and neutral endopeptidase 24.11 (NEP). A new concept combining the ideal of "prodrug" and "mixed inhibitor" was therefore developed. Given the high efficiency of β-mercaptoalkylamines as APN inhibitors and of N-(mercaptoacyl)amino acids as NEP inhibitors, compds. associating these mols. through disulfide or thioester bonds, which are known to increase lipophilicity and to favor passage across the blood-brain barrier, have been synthesized. An HPLC study indicated that the disulfide bridge was resistant to serum enzymes but was cleaved by brain membrane homogenates, suggesting that the active inhibitors were released in the central nervous system. The validity of the approach was verified by the efficient antinociceptive responses obtained in the hot plate test in mice after i.v. administration of disulfide-containing inhibitors (ED50s of from 4 to 26 mg/kg on the jump latency time). The analgesic potencies of the "mixed inhibitor-prodrug" RB 101 [H2NCH(CH2CH2SMe)CH2SSCH2CH(CH2Ph)CONHCH(CH2Ph)CO2CH2Ph] after i.v. administration were three times greater than those of

a similar combined dose of its two constitutive moieties. The separation of the two diastereoisomers constituting RB 101 showed that the analgesia has a stereochem. dependence, the (S,S,S)-isomer being more active than the (S,R,S)-isomer. Furthermore, in the tail flick test in the rat, RB 101 gave 38% analgesia at a dose of 80 mg/kg. Due to its high efficiency and its longer pharmacol. effect, RB 101 was selected for a complete study of its analgesic properties.

L3 ANSWER 104 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:408478 CAPLUS
DN 117:8478
TI Preparation of optically active glutamic acid derivatives as intermediates for analgesic
IN Wakatsuka, Hirohisa; Hashimoto, Shinsuke
PA Ono Pharmaceutical Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 03284663	A2	19911216	JP 1990-86148	19900330
PRAI	JP 1990-86148		19900330		

GI



AB A glutamic acid derivative I (R = Me; R1 = OH, R2 = Bz2)(II) cyclohexylamine salt, useful as an intermediate for the known analgesic I (R = H, R1 = NHPh, R2 = Q) (III), is prepared by reaction of a diastereomer (II) with cyclohexylamine. Thus, acylation of 3.5 g H-Glu(OMe)-OH with 3.6 g 2-benzylacryloyl chloride in the presence of NaH in dioxane and addition reaction of the resulting crude PhCH2C(:CH2)CO-Glu(OMe)-OH (.apprx.6.1 g) with thiobenzoic acid in dioxane at 0° for 18 h and at 20° for 4 h gave 9.5 g II dicyclohexylamine salt. Portionwise addition of 9.9 g the latter salt to a stirred mixture of 100 mL 5% aqueous NaHSO4 and 100 mL AcOEt, separation of the organic phase, and washing with H2O and saturated NaCl followed by evaporation gave free acid II. Refluxing II in 14.5 g mL AcOEt and 1.67 mL cyclohexylamine for 18 h followed by cooling gave 4.2 g crude crystals which were recrystd. from AcOEt to give 3.3 g II cyclohexylamine salt. The latter was converted into III in a few steps.

L3 ANSWER 105 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:236168 CAPLUS
DN 116:236168
TI Preparation of (mercaptoacylamino)acids for treatment of hypertension and congestive heart failure.
IN Haslanger, Martin F.; Neustadt, Bernard R.; Smith, Elizabeth M.

09986629

PA Schering Corp., USA
SO U.S., 22 pp. Cont.-in-part of U.S. 4,801,609.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5061710	A	19911029	US 1987-133669	19871216
	US 4801609	A	19890131	US 1987-32153	19870327
	EP 254032	A2	19880127	EP 1987-108730	19870617
	EP 254032	A3	19900905		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 08283153	A2	19961029	JP 1995-246555	19870619
	WO 8905796	A1	19890629	WO 1988-US4376	19881213
	W: AU, BB, BG, BR, DK, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU, US				
	RW: AT, BE, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	EP 322633	A1	19890705	EP 1988-120795	19881213
	EP 322633	B1	19910522		
	R: ES, GR				
	AU 8928002	A1	19890719	AU 1989-28002	19881213
	AU 615976	B2	19911017		
	EP 390839	A1	19901010	EP 1989-900561	19881213
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	JP 02503799	T2	19901108	JP 1989-500640	19881213
	HU 54979	A2	19910429	HU 1989-380	19881213
	HU 204781	B	19920228		
	AT 63741	E	19910615	AT 1988-120795	19881213
	ES 2039578	T3	19931001	ES 1988-120795	19881213
	CN 1033803	A	19890712	CN 1988-108633	19881214
	ZA 8809373	A	19900829	ZA 1988-9373	19881214
	DK 9001468	A	19900615	DK 1990-1468	19900615
	NO 9002687	A	19900615	NO 1990-2687	19900615
	US 4801609	B1	19931109	US 1991-90002282	19910214
	US 5262436	A	19931116	US 1991-741025	19910806
PRAI	US 1987-32153		19870327		
	EP 1987-108730		19870617		
	US 1986-876610		19860620		
	JP 1987-153219		19870619		
	US 1987-133669		19871216		
	EP 1988-120795		19881213		
	WO 1988-US4376		19881213		

OS MARPAT 116:236168
AB Q-CH2CH[(CH2)nR1]CONHCHR2COR3 [R1 = YC6H4XC6H4; YC6H4, YC6H4S, etc.; R2 = alkyl, (alkylsulfonyl)alkyl, (alkylsulfinyl)alkyl, etc.; R3 = (substituted) hydroxy, (substituted) amino, etc.; Q = H, alkanoyl, etc.; n = 0-2; X = bond, O, S, CH2; Y = H, alkyl, cycloalkyl, alkoxy, OH, F, etc.]and their pharmaceutically acceptable salts, useful for treatment of hypertension and congestive heart failure (no data), are prepared S-(4-Methylbenzyl)-L-cysteine Me ester hydrochloride (preparation given) was acylated with 3-(acetylthio)-2-benzylpropionic acid and the resulting diastereomeric mixture of N-[3-(acetylthio)-2-benzylpropionyl)-S-(4-methylbenzyl)-L-cysteine Me ester was treated with MeOH-1N NaOH at 0 to -5° for 6 h to give the corresponding diastereomeric mixture of N-(2-benzyl-3-mercaptopropionyl)-S-(4-methylbenzyl)-L-cysteine.

L3 ANSWER 106 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:188619 CAPLUS
DN 116:188619
TI Binding of [125I]atrial natriuretic factor to mouse lung membranes in

vivo: characterization and effects of peptidase inhibitors
AU Souque, A.; Gros, C.; Schwartz, J. C.
CS Cent. Paul Broca, Inst. Natl. Sante Rech. Med., Paris, 75014, Fr.
SO Journal of Pharmacology and Experimental Therapeutics (1992), 260(3), 1373-8
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB After i.v. injection of 125I-labeled rat atrial natriuretic factor ([125I]ANF; 99-126) in tracer dose to mice, a saturable binding to lung membranes was evidenced using a filtration assay. Anal. of the membrane-bound radioactivity by high-pressure liquid chromatog. indicated that it corresponded to the intact hormone in sinorphan-treated mice. [125I]rANF binding was inhibited completely by i.v. administration of rANF with an ED50 of 1.0 nmol/kg, a value obtained in sinorphan-treated mice. SC 416,542, an ANF analog with a four amino acid deletion in its ring, representing a selective ligand of ANF clearance receptors, was as potent as rANF in inhibiting the in vivo binding. By contrast, ANF fragments produced by enkephalinase (EC 3.4.24.11, membrane metalloendopeptidase) were less potent or even inactive in competing with [125I]rANF. It is concluded that [125I]rANF binding to lung membranes in vivo occurs to clearance receptors. [125I]rANF binding was enhanced by more than 2-fold in mice receiving enkephalinase inhibitors such as sinorphan and, although to a lesser extent, aminopeptidase inhibitors; on the other hand inhibitors of a variety of other peptidases were ineffective. These data confirm by a novel approach that enkephalinase plays a key role in the inactivation of circulating ANF. Hence, the in vivo binding test can be used to assess the activity of clearance receptor ligands and peptidase inhibitors, two classes of drugs affecting ANF metabolism, with potential clin. utility in cardiovascular and salt-retaining diseases.

L3 ANSWER 107 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:174699 CAPLUS
DN 116:174699
TI Potent and systemically active aminopeptidase N inhibitors designed from active-site investigation
AU Fournie-Zaluski, Marie Claude; Coric, Pascale; Turcaud, Serge; Bruetschy, Luce; Lucas, Evelyne; Noble, Florence; Roques, Bernard P.
CS Dep. Chim. Org., Univ. Rene Descartes, Paris, 75270, Fr.
SO Journal of Medicinal Chemistry (1992), 35(7), 1259-66
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
AB Derivs. of amino acids bearing various zinc-coordinating moieties e.g. H2NCHRCH2R1 [R = CH2Ph, CH2C6H4OH-4, 2-naphthylmethyl, cyclohexylmethyl, CH2OCH2Ph, CH2SCH2Ph, CH2CHMe2, CH2CH2SMe, CH2SMe, CH2SCMe3, CH2S(O)Me, CH2CH2S(O)Me; R1 = SH, CO2H, CONHOH, PO3H2] were synthesized and tested for their ability to inhibit aminopeptidase N (I). Among them, β-amino thiols were the most efficient with ED50 = 11-50 nM. These results suggest that the S1 subsite of I is a deep but not very large hydrophobic pocket, optimally fitting side chains of moderate bulk endowed with some degree of freedom. The i.v. administration of the inhibitors, alone, did not induce antinociceptive responses in the hot plate test in mice. However, in presence of 10 mg/kg acetorphan, a prodrug of the neutral endopeptidase inhibitor thiorphan, these compds. gave a large increase in the jump latency time with ED50 = 2 and 2.4 mg/kg for (H2NCHRCH2S)2 [R = CH2CH2SMe, CH2CH2S(O)Me], resp. These results show that the disulfide forms of β-amino thiols are efficient prodrugs of aminopeptidase N inhibitors capable of crossing the blood-brain barrier.

L3 ANSWER 108 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:951 CAPLUS

09986629

DN 116:951
TI Desensitization of μ-opioid receptors does not modify the analgesia induced by an enkephalinase inhibitor
AU Bousselmame, Rachida; Michael-Titus, Adina; Costentin, Jean
CS Unite Neuropsychopharmacol. Exp., Fac. Med. Pharm. Rouen, Saint-Etienne du Rouvray, 76800, Fr.
SO European Journal of Pharmacology (1991), 203(2), 295-7
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Acetorphan, an enkephalinase inhibitor, or morphine was injected in mice which had received saline or morphine (32 mg/kg s.c. twice a day on 8 consecutive days) chronically. In the hot-plate test, the analgesia (increase in jump latency) induced by morphine (2 mg/kg, i.p.) or by the μ selective opioid agonist, DAGO, (1.5, 3, or 6 ng/mouse i.c.v.), was significant in the saline group but was strongly decreased in morphine-pretreated mice. In contrast the analgesic effect of acetorphan (5 mg/kg, i.v.) or of the δ selective opioid agonist [D-Pen2,D-Pen5]enkephalin (DPDPE) (0.75, 1.5, or 3 μg/mouse i.c.v.) was similar in both groups. These results suggest that the enkephalins protected by acetorphan act on the δ receptor site to produce antinociception.

L3 ANSWER 109 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:550297 CAPLUS
DN 115:150297
TI Chronic inhibition of enkephalinase induces changes in the antinociceptive and locomotor effects of the enkephalinase inhibitor acetorphan in rats
AU Bousselmame, R.; Eustache, M.; Michael-Titus, A.; Costentin, J.
CS Unite Neuropsychopharmacol. Exp., Fac. Med. Pharm. Rouen, Saint Etienne de Rouvray, 76803, Fr.
SO Neuropharmacology (1991), 30(8), 865-70
CODEN: NEPHBW; ISSN: 0028-3908
DT Journal
LA English
AB The enkephalinase inhibitor thiorphan was infused intracerebroventricularly in rats during 14 days (25 μg/5 μL/h), inducing an average inhibition of cerebral enkephalinase of about 65%. Animals were tested during the infusion for their response to acetorphan, a parenterally active derivative of thiorphan. When administered i.v. on day 8 of the infusion, acetorphan (5 mg/kg) significantly increased locomotion in chronic saline-infused rats but not in animals receiving thiorphan. Furthermore, when injected at the same dose on day 10, acetorphan did not modify the latency to jump, in the hot plate test, in thiorphan-treated rats, whereas it elicited a significant analgesia in chronic saline-treated controls. These data show that the effects induced by the administration of an enkephalinase inhibitor were diminished after a period of chronic inhibition of the enzyme, suggesting the development of tolerance.

L3 ANSWER 110 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:199694 CAPLUS
DN 114:199694
TI Method and kit for neurochemical promotion of the effects of low current transcranial electrostimulation to enhance the ability of the central nervous system to provide relief from pain, addiction withdrawal
IN Skolnick, Malcolm H.; Malin, David H.
PA USA
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English

09986629

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9101756	A1	19910221	WO 1990-US4443	19900808
	W: AU, CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	AU 9061709	A1	19910311	AU 1990-61709	19900808
PRAI	US 1989-392868		19890811		
	WO 1990-US4443		19900808		

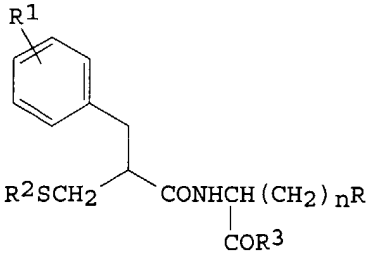
AB When various neuroactive chemical promoters are administered concomitantly with transcranial electrostimulation (TE), a more intense and prolonged physiol. result is achieved than was expected. A method of providing relief from painful or stressful stimuli, or remediating imbalances or deficiencies in neuroactive substances that modulate neurohumoral mechanisms, involves concomitant administration of a neuroactive chemical promoter and TE. This combination enhances the ability of the central nervous system to provide relief from, e.g., pain, addiction withdrawal, anxiety, and depression. Kits and compns. are also disclosed. Rats receiving both TE (10 Hz, 10 μA, 2 ms pulse width, 30 min) and thiorphan (enkephalinase inhibitor) had significantly greater analgesia than rats receiving drug alone, TE alone, or saline. Morphine addicted rats receiving TE and 10 mg proglumide/kg in saline had significantly fewer abstinence signs.

L3 ANSWER 111 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:515863 CAPLUS
DN 113:115863
TI Preparation of N-(mercaptoalkanoyl)methionine analogs as antihypertensives
IN Czarniecki, Michael F.; Lehman, Laura S.
PA Schering Corp., USA
SO Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 355784	A1	19900228	EP 1989-115439	19890822
	R: ES, GR				
	WO 9002117	A1	19900308	WO 1989-US3546	19890822
	W: AU, BB, BG, BR, DK, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU				
	RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	AU 8940563	A1	19900323	AU 1989-40563	19890822
PRAI	US 1988-235587		19880824		
	WO 1989-US3546		19890822		

OS MARPAT 113:115863
GI



I

AB The title compds. [I; n = 0-4; R = CH(SR4)SR5, C(SR6)(SR7)SR8, Q; R1 = 1-3 substituents selected from the group consisting of H, halo, alkyl, cycloalkyl, HO, aryl aryloxy, cyano, etc.; R2 = H, Ac, Bz, etc.; R3 = OR12, NR12R13, OCHR14CONR12R13; R4-R10 = alkyl, aralkyl, cycloalkylalkyl, etc.; R12, R13 = H, (substituted) alkyl, etc.], being angiotensin converting enzyme inhibitors and therefore useful as antihypertensives (no data), were prepared via N-acylation of the appropriate amino acid derivative with the appropriate carboxylic acid. (S)-MeO2CCH(NH2)CH2CH(SMe)2 (preparation given) was condensed with AcSCH2CH(CH2Ph)CO2H to give I [n = 1; R = CH(SMe)2, R1 = H, R2 = Ac, R3 = OMe]. Tablets, injections, etc., were formulated.

L3 ANSWER 112 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:418384 CAPLUS
DN 113:18384
TI Stereoselective protection of exogenous and endogenous atrial natriuretic factor by enkephalinase inhibitors in mice and humans
AU Lecomte, Jeanne Marie; Baumer, Philippe; Lim, Catherine; Duchier, Jacques; Cournot, Antoine; Dussaule, Jean Claude; Ardaillou, Raymond; Gros, Claude; Chaignon, Beatrice; et al.
CS Lab. Bioprojet, Paris, 75003, Fr.
SO European Journal of Pharmacology (1990), 179(1-2), 65-73
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The relative potencies of sinorphan and retorphan, the S- and R-enantiomers of acetorphan a potent inhibitor of enkephalinase (E.C. 3.4.34.11), to inhibit membrane metalloendopeptidase in vivo and to protect exogenous and endogenous atrial natriuretic factor (ANF) after oral administration were compared. In mice, sinorphan was 2-3-fold as potent as retorphan in inhibiting the specific in vivo binding of [3H]acetorphan to kidney enkephalinase. The same potency ratio was found for the enhancement of TCA-precipitated radioactivity in kidneys of mice that had received 125I-labeled ANF, which is used as a test for the protection of the hormone against inactivation in vivo. In 9 healthy human volunteers who had received a low oral dosage of sinorphan or retorphan in a double-blind, placebo-controlled, randomized trial, sinorphan was also 2-3-fold more potent than retorphan in inhibiting plasma enkephalinase activity. These effects were accompanied by a related rise in plasma ANF immunoreactivity, which also reflected the difference in the effectiveness of the 2 compds. Sinorphan was also more potent than retorphan in enhancing urinary cGMP excretion and Na excretion in 5 of these subjects. These data indicate that, in humans as in rodents, enkephalinase plays a crucial role in the inactivation of ANF, its partial inhibition in vivo being accompanied by a significant protection of the exogenous or endogenous hormone as well as by typical ANF-like responses. Thus, orally administered sinorphan appears to be a promising compound for therapeutic use in cardiovascular and renal diseases in which ANF has been postulated to exert beneficial effects.

L3 ANSWER 113 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:401134 CAPLUS
DN 113:1134
TI Diuretic and natriuretic responses in rats treated with enkephalinase inhibitors
AU Bralet, Jean; Mossiat, Claude; Lecomte, Jeanne Marie; Charpentier, Stephane; Gros, Claude; Schwartz, Jean Charles
CS Lab. Pharmacodyn., Fac. Pharm. Dijon, Dijon, 21000, Fr.
SO European Journal of Pharmacology (1990), 179(1-2), 57-64
CODEN: EJPHAZ; ISSN: 0014-2999

09986629

DT Journal
LA English
AB Rat atrial natriuretic factor (125I-rANF, 99-126) is hydrolyzed by pure enkephalinase (EC 2.4.24.11) in vitro at a rate similar to that of 125I-hANF. TCA-precipitated radioactivity was elevated in the kidneys of rats pretreated with acetorphan, an enkephalinase inhibitor, and receiving 125-I-rANF, indicating that the exogenous hormone was protected against degradation A single oral administration of acetorphan elicited diuretic and natriuretic effects in conscious normotensive rats and natriuretic effects in spontaneously hypertensive rats, effects which were not accompanied by changes in kaliuresis. The diuretic and natriuretic effects were still observed in conscious normotensive rats after 3 days of repeated administration of the drug. In conscious or anesthetized rats in which volume expansion was elicited by hydroelectrolytic loads, the initial rate of urinary elimination of water and Na was nearly doubled by treatment with enkephalinase inhibitors. This effect was prevented by coadministration of an ANF antiserum, which suggest that the effect was mediated by endogenous ANF. These various observations suggest that enkephalinase inhibitors protect endogenous ANF from degradation and thereby enhance the typical renal effects of the hormone.

L3 ANSWER 114 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:401133 CAPLUS
DN 113:1133
TI Inactivation of atrial natriuretic factor in mice in vivo: crucial role of enkephalinase (EC 3.4.24.11)
AU Gros, Claude; Souque, Anny; Schwartz, Jean Charles
CS Unit. Neurobiol. Pharmacol., INSERM, Paris, 75014, Fr.
SO European Journal of Pharmacology (1990), 179(1-2), 45-56
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Simple tests were developed to study the peptidases responsible for the hydrolysis of atrial natriuretic factor (ANF) in mice in vivo and to assess the effects of peptidase inhibitors. In mice injected with 125I-labeled ANF in low amts. the radioactivity present in kidney, a major target organ for the hormone, was analyzed by HPLC, precipitation with TCA, and in a membrane binding assay. All 3 parameters indicated a rapid inactivation of the hormone: 20 s after injection of 125I-labeled ANF the intact hormone represented < 20% of the total kidney radioactivity. Oral pretreatment with acetorphan, a potent enkephalinase inhibitor resulted in a marked increase in the amount of intact 125I-labeled ANF (6-fold), TCA-precipitated (5-fold), and membrane bound radioactivity (4-fold) in the kidney: the total kidney radioactivity was enhanced by .apprx.2-fold. A similar protective effect was observed with other enkephalinase inhibitors, i.e. thiorphan and kelatorphan: the later was effective at a 10-fold higher dosage. In contrast, a large variety of inhibitors of metallo-, cysteine, serine and aspartic proteinases had no or only marginal effects. Instead, captopril, an angiotensin-converting enzyme inhibitor, reduced total and TCA-precipitable radioactivity in the kidneys. Aminopeptidase inhibitors, used either alone or in conjunction with acetorphan, displayed significant but limited protective effects. The crucial role of enkephalinase in ANF inactivation in vivo suggests that inhibitors of this peptidase could be used in a novel therapeutic approach to cardiovascular or renal diseases by protecting endoenous ANF.

L3 ANSWER 115 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:179882 CAPLUS
DN 112:179882
TI Thioacylamino acids as enkephalinase inhibitors
IN Kawamura, Masanori; Arai, Yoshinobu; Aishita, Hideki

09986629

PA Ono Pharmaceutical Co., Ltd., Japan
SO Eur. Pat. Appl., 65 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 341081	A2	19891108	EP 1989-304564	19890505
	EP 341081	A3	19901227		
	EP 341081	B1	19950705		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 02209861	A2	19900821	JP 1989-112067	19890502
	JP 05059114	B4	19930830		
	CA 1330613	A1	19940705	CA 1989-598418	19890502
	US 5017589	A	19910521	US 1989-347673	19890505
	ES 2076959	T3	19951116	ES 1989-304564	19890505
	US 5202340	A	19930413	US 1991-679214	19910402
	JP 06179649	A2	19940628	JP 1992-216593	19920723
	JP 06092358	B4	19941116		
	US 5317021	A	19940531	US 1992-971229	19921104
PRAI	JP 1988-109191		19880506		
	JP 1988-249433		19881003		
	US 1989-347673		19890505		
	US 1991-679214		19910402		

OS MARPAT 112:179882
GI For diagram(s), see printed CA Issue.
AB R4SCH2CH(CH2R3)CONHCH[(CH2)nCO2R1](CH2)nCONHR2 [I; R1 = H, alkyl; R2 = (substituted) (hetero)cyclyl; R3 = (substituted) Ph, cycloalkyl; R4 = H, alkylcarbonyl, (substituted) benzoyl, pyridylcarbonyl, diphenylacetyl, oxoisobenzofuryl, etc.; when m = 0, n = 1-4; when n = 0, m = 1-4], useful as enkephalinase inhibitors, were prepared Thus, RS-AcSCH2CH(CH2Ph)COCl (preparation given) in CH2Cl2 was added to L-H2NCH(CH2CH2CO2CH2Ph)CONHPh.CF3CO2H (preparation given) in pyridine/CH2Cl2 with ice cooling. The mixture was stirred 15 min to give the corresponding amide, which was deacetylated with LiOH.H2O in THF/DME/H2O to give II. II at 10 mg/kg i.p. in rats reduced bradykinin-induced biting response in 4 of 5 rats after 40 min.

L3 ANSWER 116 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:158967 CAPLUS
DN 112:158967
TI Preparation of mercapto-acylamino acid antihypertensives
IN Haslanger, Martin F.; Neustadt, Bernard Ray; Smith, Elizabeth Melva
PA Schering Corp., USA
SO Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 322633	A1	19890705	EP 1988-120795	19881213
	EP 322633	B1	19910522		
	R: ES, GR				
	US 5061710	A	19911029	US 1987-133669	19871216
	AT 63741	E	19910615	AT 1988-120795	19881213
PRAI	US 1987-133669		19871216		
	US 1987-32153		19870327		
	EP 1987-108730		19870617		
	EP 1988-120795		19881213		

AB QSCH2CH[(CH2)nR1]CONHCHR2COR3 [I; R1 = YC6H4, YC6H4S, YC6H4O, naphthyl, furyl, thienyl, benzofuryl, benzothienyl, Ph2CH, etc.; R2 =

R4(CH2)kSOn(CH2)q, R5O2C(CH2)q; R3 = OR7, NR7R8, NHCHR9CONR7R8, NHCHR9CO2R7, OCHR9CONR7R8; R4 = alkenyl, alkoxy, alkylthio, OH; R5 = dihydroalkyl, dialkoxyalkyl, alkoxyalkoxyalkyl, haloalkyl, etc.; R7, R8 = H, R5, alkyl, hydroxyalkyl, aminoalkyl, arylalkyl, etc.; R7R8N = (substituted) heterocyclyl; R9 = H, alkyl, carboxyalkyl, guanidinoalkyl, indolylalkyl, mercaptoalkyl, etc.; R10 = alkyl, hydroxyalkyl, alkoxyalkyl, diaminoalkyl, naphthyl, furyl, thienyl, pyridyl, etc.; Q = H, R10CO; YY1 = H, alkyl, cycloalkyl, alkoxy, OH, F, Cl, Br, cyano, CH2NH2, CO2H, Ph, etc.; k = 1-3; m,n = 0-2; q = 1-4], useful as antihypertensives and adjuvants for atrial natriuretic factors or angiotencin converting enzyme inhibitors, were prepared Thus, a mixture of 3-benzoylthio-2(S)-benzylpropionic acid, S-allyl-(R)-cysteinamide hydrochloride, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole, and N-methylmorpholine was stirred 20 h in DMF to give N-[3-benzoylthio-2(S)-benzylpropionyl]-S-allyl-(R)-cysteinamide.

L3 ANSWER 117 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:56701 CAPLUS
DN 112:56701
TI Preparation of enantiomeric derivatives of amino acids as analgesics and cardiovascular agents
IN Duhamel, Pierre; Duhamel, Lucette; Danvy, Denis; Plaquevent, Jean Christophe; Giros, Bruno; Gros, Claude; Schwartz, Jean Charles; Lecomte, Jeanne Marie
PA Societe Civile Bioprojet, Fr.
SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 318377	A2	19890531	EP 1988-402944	19881124
	EP 318377	A3	19900307		
	EP 318377	B1	19930825		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	FR 2623498	A1	19890526	FR 1987-16239	19871124
	FR 2623498	B1	19900406		
	US 5208255	A	19930504	US 1988-274884	19881122
	JP 02000161	A2	19900105	JP 1988-297144	19881124
	JP 2529172	B2	19960828		
	AT 93518	E	19930915	AT 1988-402944	19881124
	ES 2059554	T3	19941116	ES 1988-402944	19881124
	US 5136076	A	19920804	US 1990-540168	19900619
	US 5296509	A	19940322	US 1993-11690	19930201
	US 5331008	A	19940719	US 1993-11672	19930201
	JP 08059606	A2	19960305	JP 1995-139872	19950515
	JP 2537159	B2	19960925		
PRAI	FR 1987-16239		19871124		
	US 1988-274884		19881122		
	EP 1988-402944		19881124		

OS CASREACT 112:56701; MARPAT 112:56701
AB Enantiomeric AcSCH2CH(CH2Ph)CONHCHR2CO2R1 [R1 = Me, CH2Ph; R2 = H, Me], inhibitors for enkephalinase and angiotensin converting enzyme, useful as analgesics and cardiovascular agents, are prepared (+)-(R)-AcSCH2CH(CH2Ph)CO2H, obtained by resolution of (±)-AcSCH2CH(CH2Ph)CO2H via diastereomeric salt formation with (+)-ephedrine, was amidated with H2NCH2CO2CH2Ph to give (+)-(R)-AcSCH2CH(CH2Ph)CONHCH2CO2CH2Ph, which showed in vitro inhibition of enkephalinase and angiotensin converting enzyme at 2 and 5000 nM, resp.

L3 ANSWER 118 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN

09986629

AN 1990:56688 CAPLUS
DN 112:56688
TI Amino acid and peptide derivatives as inhibitors of neutral endopeptidase and their use as antihypertensives and diuretics
IN Delaney, Norma G.; Gordon, Eric M.; DeForrest, Jack M.; Cushman, David W.
PA E. R. Squibb and Sons, Inc., USA
SO Ger. Offen., 53 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3819539	A1	19881222	DE 1988-3819539	19880608
	CA 1337400	A1	19951024	CA 1988-566338	19880509
	GB 2207351	A1	19890201	GB 1988-13372	19880606
	GB 2207351	B2	19910918		
	FR 2616070	A1	19881209	FR 1988-7626	19880608
PRAI	US 1987-59072		19870608		

OS MARPAT 112:56688
AB Administration of ≥1 inhibitor of neutral endopeptidase, optionally together with an antihypertensive agent such as an angiotensin-converting enzyme inhibitor, produces diuresis, natriuresis, and lowering of the blood pressure. The endopeptidase inhibitor is an amino acid or peptide derivative or related compound with a structure represented by any of 10 Markush line formulas, e.g. R4S(CH2)2CHR2CONHCHR1(CH2)nCO2R3 [R1, R2 = H, (substituted) alkyl, cycloalkyl, (substituted) aryl or aralkyl; R3 = H, lower alkyl, PhCH2, Ph2CH, ion; R4 = H, acyl; m = 0, 1; n = 0-15]. N-[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]-L-leucine (I) was prepared by reaction of 3-acetylthio-2-benzylpropionic acid with oxalyl chloride, then with L-leucine Me ester.HCl, and sapon; I inhibited rat kidney neutral endopeptidase in vitro by 50% at 0.0066 μM, decreased the mean arterial pressure in DOCA-hypertensive rats by 65 mm Hg at 300 μmol/kg i.v., and increased urinary Na+ excretion 2.4-fold in rats at 100 mg/kg i.v.

L3 ANSWER 119 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:55259 CAPLUS
DN 112:55259
TI N-Substituted phenyl(mercapto)propanamides as analgesics and their preparation
IN Mimura, Tetsutaro; Nakamura, Yasuhisa; Nishino, Junko; Sawayama, Tadahiro; Sasagawa, Takashi; Deguchi, Takashi; Nakamura, Hideo
PA Dainippon Pharmaceutical Co., Ltd., Japan
SO Eur. Pat. Appl., 86 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 318859	A2	19890607	EP 1988-119666	19881125
	EP 318859	A3	19900816		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	DK 8806761	A	19890604	DK 1988-6761	19881202
	AU 8826508	A1	19890608	AU 1988-26508	19881202
	AU 614558	B2	19910905		
	HU 49115	A2	19890828	HU 1988-6159	19881202
	HU 201005	B	19900928		
	JP 02160760	A2	19900620	JP 1988-306442	19881202
PRAI	JP 1987-306763		19871203		
	JP 1988-200697		19880810		

09986629

AB The title compds. R1CHWCH(CH2R2)CONHXR3 [I; R1 = mercapto, group convertible into mercapto; W = H, alkyl, aralkyl; R2 = (substituted) aryl, heterocyclic group, etc.; X = cycloalkylene, cycloalkylidene, phenylene which may have substituents or may be fused with a ring; R3 = carboxy, group convertible to carboxy] and pharmaceutically acceptable salts thereof, useful as enkephalinase-inhibiting analgesics, were prepared A mixture of 3-amino-5-methylbenzoic acid, Et3N, and 2-acetylthiomethyl-3-phenylpropionyl chloride in THF-H2O was stirred 2 h at room temperature to give 3-[(2-acetylthiomethyl-3-phenylpropionyl)amino]-5-methylbenzoic acid (II). II exhibited an oral ED50 of 22.3 mg/kg in a phenylquinone-induced writhing test using mice.

L3 ANSWER 120 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:632590 CAPLUS
DN 111:232590
TI Heterocyclic mercaptopropanamide derivatives as oral analgesics
IN Mimura, Tetsutaro; Nakamura, Yukihisa; Nishino, Junko; Sawayama, Tadahiro; Sasagawa, Takashi; Deguchi, Takashi; Nakamura, Hideo
PA Dainippon Pharmaceutical Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01149763	A2	19890612	JP 1987-310708	19871207

PRAI JP 1987-310708 19871207

AB R1CH2CH(CH2R2)CONHCH2R3 [R1 = SH, groups forming SH in organs; R2 (un)substituted pyridyl, (N-substituted) morpholinyl, C6H4NR4R5, (CH2)nNR4R5; R3 = CO2H, groups forming CO2H in organs; R4, R5 = H, lower alkyl; R4R5 may form a ring; n = 1, 2] and their salts are prepared Thus, condensation of 25 g isonicotinaldehyde and 36.8 g di-Et malonate gave 57.5 g di-Et 4-pyridinylmethylenemalonate, which was hydrogenated over Pd/C, hydrolyzed, and then treated with HCHO and Me2NH to give 15 g 2-(4-pyridinylmethyl)acrylic acid (I). Then, 15 g I and 10 g AcSH were stirred at 50° for 15 min to give 5.5 g 2-acetylthiomethyl-3-(4-pyridinyl)propionic acid, 1.5 g of which was treated with 2.1 g glycine benzyl ester p-toluenesulfonate in presence of Et3N and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl at 0° for 0.5 h and at room temperature for 2 h to give 3.5 g benzyl [2-acetylthiomethyl-3-(4-pyridinyl)propionyl]aminoacetate (II). II showed 80.8% analgesic activity in writhing test at 200 mg/kg p.o. in rats.

L3 ANSWER 121 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:609687 CAPLUS
DN 111:209687
TI Protection of atrial natriuretic factor against degradation: diuretic and natriuretic responses after in vivo inhibition of enkephalinase (EC 3.4.24.11) by acetorphan
AU Gros, Claude; Souque, Anny; Schwartz, Jean Charles; Duchier, Jacques; Cournot, Antoine; Baumer, Philippe; Lecomte, Jeanne Marie
CS Unite Neurobiol. Pharmacol., Cent. Paul Broca, Paris, 75014, Fr.
SO Proceedings of the National Academy of Sciences of the United States of America (1989), 86(19), 7580-4
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Atrial natriuretic factor (ANF) might be beneficial in several cardiovascular disorders, but its poor oral absorption and rapid inactivation in vivo have so far prevented its use in therapeutics. The role of enkephalinase (membrane metalo-endopeptidase, EC 3.4.24.11) in the

in vivo inactivation of ANF was assessed in mice and healthy human volunteers by evaluating the effects of acetorphan, a potent inhibitor. In mice, the degradation of 125I-labeled ANF was markedly delayed, as shown by the levels of the intact peptide in the plasma and the kidney, a major target organ. The effect of acetorphan was due to the inhibition of enkephalinase activity, since it occurred at an ED50 very close to this drug's ID50 for the inhibition of the specific binding of radioactive material to the kidney or lung peptidase that was measured after administration of [3H]acetorphan. The effects of acetorphan were also studied in healthy human volunteers by using a randomized double-blind, placebo-controlled design. Oral administration of acetorphan elicited a lasting elevation of plasma ANF-like immunoreactivity, with a time course parallel to that of the inhibition of plasma enkephalinase activity. These effects were accompanied by significant increases in urinary volume and Na excretion, 2 well-established renal responses to ANF peptides. Apparently, enkephalinase plays a critical role in ANF degradation in vivo, and its inhibition enhances the levels of circulating endogenous ANF, which, in turn, results in diuresis and natriuresis. Enkephalinase inhibition may constitute another therapeutic approach to the treatment of cardiovascular diseases, such as congestive heart failure or essential hypertension, on which ANF is postulated to have a beneficial effect.

L3 ANSWER 122 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:450240 CAPLUS
DN 111:50240
TI Naloxone-reversible inhibition of gallbladder mucosal fluid secretion in experimental cholecystitis in the cat by acetorphan, an enkephalinase inhibitor
AU Jivegaard, L.; Pollard, H.; Moreau, J.; Schwartz, J. C.; Thune, A.; Svanvik, J.
CS Dep. Surg., Sahlgrenska Hosp., Goeteborg, Swed.
SO Clinical Science (1989), 77(1), 49-54
CODEN: CSCIAE; ISSN: 0143-5221
DT Journal
LA English
AB By using [3H][D-Ala2-Leu5]enkephalin as a substrate, enkephalinase activity, immunopptd. by a monoclonal antibody directed against the rabbit kidney enzyme, was demonstrated in the feline gallbladder. By using the same antibody in an 125I-labeled form, the peptidase was immunolocalized by autoradiog., mainly in the epithelium. In exptl. cholecystitis, elicited by implantation of human gall-stones into the cat gallbladder, the continuous fluid secretion into the lumen was inhibited by exogenous enkephalins. Acetophan, an enkephalinase inhibitor, blocked fluid secretion by the inflamed gallbladder via a naloxone-sensitive mechanism, but did not affect fluid transport in the normal gallbladder. The drug also transiently contracted the gallbladder and increased bile outflow from the liver. Apparently, acetorphan, by reducing the degradation of endogenous enkephalins in the inflamed gallbladder, decreases fluid secretion by the epithelium and enkephalinase inhibitors may find clin. applications in acute cholecystitis.

L3 ANSWER 123 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:417524 CAPLUS
DN 111:17524
TI Assessment of the abuse potential of acetorphan, an enkephalinase inhibitor
AU Knisely, Janet S.; Beardsley, Patrick M.; Aceto, Mario D.; Balster, Robert L.; Harris, Louis S.
CS Med. Coll. Virginia, Virginia Commonw. Univ., Richmond, VA, 23298-0613, USA
SO Drug and Alcohol Dependence (1989), 23(2), 143-51
CODEN: DADEDV; ISSN: 0376-8716

09986629

DT Journal
LA English
AB The discriminative stimulus properties, reinforcing effects and phys. dependence potential of acetorphan, a parenterally-active enkephalinase (E.C. 3.4.21.11) inhibitor, were assessed in the present studies. Rats trained to discriminate 2 mg/kg morphine from saline did not generalize to acetorphan at any dose tested (5-50 mg/kg). Acetorphan also had minimal reinforcing effects in rhesus monkeys. When acetorphan was substituted for cocaine, one dose (300 μg/kg) maintained responding somewhat above the range of vehicle values in only two of the four monkeys tested. In phys. dependence studies, acetorphan also failed to produce opioid-like effects. In morphine-dependent monkeys and rats, acetorphan failed to suppress withdrawal. Addnl., there were no overt withdrawal signs observed following the termination of chronic acetorphan infusion in the rat. Together, these results indicate that acetorphan appears to have minimal abuse potential.

L3 ANSWER 124 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:205560 CAPLUS
DN 110:205560
TI Augmented analgesic effects of enkephalinase inhibitors combined with transcranial electrostimulation
AU Malin, D. H.; Lake, J. R.; Hamilton, R. F.; Skolnick, M. H.
CS Programs Behav. Biol. Sci., Univ. Houston, Houston, TX, 77058, USA
SO Life Sciences (1989), 44(19), 1371-6
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB The analgesic effects of very-low current transcranial electrostimulation are nalaxone-reversible and, thus, presumably mediated by endogenous opioid activity. Blocking enkephalinase activity by intracerebroventricular thiophan or i.p. acetorphan increased the analgesic effect of electrostimulation as measured by the 50° wet tail flick test. Rats receiving both drug and electrostimulation displayed more analgesia than rats receiving electrostimulation and injection vehicle alone, rats receiving drug and sham stimulation, or rats receiving vehicle and sham stimulation.

L3 ANSWER 125 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:153275 CAPLUS
DN 110:153275
TI Enkephalinase inhibitors and their use as animal growth promoters
IN Bueno, Lionel
PA Institut National de la Recherche Agronomique, Fr.
SO Fr. Demande, 16 pp.
CODEN: FRXXBL
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI FR 2607701	A1	19880610	FR 1986-17148	19861208
PRAI FR 1986-17148		19861208		

AB Enkephalinase inhibitors can be used as animal growth promoters. Young rats were administered 0.25 mg acetorphan daily for 8 days. The average daily weight gain was 5.08 g, whereas it was 4.02 g/day for nontreated controls. Food consumption increased by 9.4% in the acetorphan-treated rats; the ratio of consumed food/body weight gain was 3.68 g food/g weight gain for treated animals and 4.25 g food/g weight gain for nontreated animals.

L3 ANSWER 126 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:18466 CAPLUS

09986629

DN 110:18466
TI Evaluation of enkephalinase inhibition in the living mouse, using [3H]acetorphan as a probe
AU De la Baume, S.; Brion, F.; My Dam Trung Tuong; Schwartz, J. C.
CS Lab. Physiol., Univ. Rene Descartes, Paris, 75006, Fr.
SO Journal of Pharmacology and Experimental Therapeutics (1988), 247(2), 653-60
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB A novel in vivo binding test was developed in order to evaluate the degree of occupancy of enkephalinase (EC 3.4.24.11), a membrane-bound metallopeptidase, in cerebral and peripheral tissues of mice treated with enkephalinase inhibitors. The probe selected for this purpose was the prodrug [3H]acetorphan, a lipophilic diesterefied derivative of the potent enkephalinase inhibitor thiorphan readily releasing the latter by tissue hydrolysis. In order to validate the in vivo binding assay, [3H]thiorphan binding to membranes was first studied in vitro. [3H]thiorphan binding to cerebral and peripheral tissues (lung and kidney) was saturable over a low nonspecific binding, occurring with a KD of 0.6 nM consistent with the Ki of the compound as an enkephalinase inhibitor. [3H]thiorphan binding varied largely among various tissues and was highly correlated with the catalytic activity of enkephalinase, thus indicating a selective labeling of the peptidase. After the i.v. administration of [3H]acetorphan to mice, a large fraction of the radioactivity remained bound to membranes isolated by a rapid filtration assay. In vivo binding generated by [3H]acetorphan was saturable, with maximum binding sites values which were in rather good agreement with corresponding maximum binding sites values of [3H]thiorphan binding in vitro, particularly in brain. Specific in vivo binding varied largely among tissues and generally reflected the abundance of enkephalinase mols. in the latter. In vivo binding was inhibited by enkephalinase inhibitors, e.g. thiorphan, acetorphan or phosphoramidon or dipeptides, e.g. Phe-Gly or Phe-Ala. The relative in vivo potencies of these compds., assessed by determination of either their ID50 or the percentage of inhibition at a single dosage, largely differed among tissues and appeared to reflect both their relative potencies to inhibit the enzyme in vitro and their tissue distribution. It is concluded that in vivo binding generated by [3H]acetorphan selectively occurs to enkephalinase mols. and that this test might be useful to assess the in vivo potency and tissue selectivity of enkephalinase inhibitors.

L3 ANSWER 127 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:622248 CAPLUS
DN 109:222248
TI Thiorphan and acetorphan inhibit gastric secretion by a central, non-opioid mechanism in the rat
AU Chicau-Chovet, Maria; Dubrasquet, Marcelle; Chariot, Jacques; Tsocas, Annick; Lecomte, Jeanne Marie; Roze, Claude
CS Fac. Med. X, Paris, F75018, Fr.
SO European Journal of Pharmacology (1988), 154(3), 247-54
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Thiorphan and its prodrug, acetorphan, are 2 inhibitors of enkephalinase (EC 3.4.24.11), a membrane-bound peptidase which plays an important role in the metabolic degradation of enkephalins. Since exogenous opioids have been reported to both stimulate and inhibit gastric secretion, the effects of thiorphan and acetorphan were studied in conscious rats equipped with chronic gastric fistulas. While i.v. thiorphan had no effect, both i.c.v. thiorphan and i.v. acetorphan potently inhibited the basal gastric acid output and the acid output stimulated by pentagastrin. Conversely,

neither drug affected the histamine- or methacholine-induced stimulation of acid secretion. Neither thiorphan or acetorphan had any effect on the acid secretion stimulated by a combination of pentagastrin and acetylcholine in vagotomized rats. Th results strongly suggest that both drugs inhibit gastric secretion through an effect at the level of the central nervous system, which decreases the vagal drive to the stomach. However, the effects of thiorphan and acetorphan were not prevented by naloxone. This is at variance with most of the effects of these drugs reported to date, including the inhibition of gastric secretion in cats. Furthermore, these effects were observed at doses which could inhibit other enzymes apart from enkephalinase. This suggests that the antisecretory action in rats is related to the protection of some non-opioid peptide(s) from degradation In conclusion, both peptidase inhibitors inhibit gastric secretion of the rat through a central mechanism involving unknown, non-opioid peptide(s).

L3 ANSWER 128 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:448448 CAPLUS
DN 109:48448
TI Neutral metalloendopeptidase inhibitors in the treatment of hypertension, compositions and kits containing the inhibitors, manufacture of the compositions, compounds of the compositions and their preparation
IN Haslanger, Martin F.; Sybertz, Edmund, Jr.; Neustadt, Bernard R.; Smith, Elizabeth M.
PA Schering Corp., USA
SO Eur. Pat. Appl., 167 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 254032	A2	19880127	EP 1987-108730	19870617
	EP 254032	A3	19900905		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	US 4749688	A	19880607	US 1986-876610	19860620
	US 4801609	A	19890131	US 1987-32153	19870327
	EP 566157	A1	19931020	EP 1993-107499	19870617
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	FI 8702720	A	19871221	FI 1987-2720	19870618
	AU 8774458	A1	19871224	AU 1987-74458	19870618
	AU 602701	B2	19901025		
	ZA 8704413	A	19880224	ZA 1987-4413	19870618
	HU 44940	A2	19880530	HU 1987-2786	19870618
	IL 82908	A1	19910916	IL 1987-82908	19870618
	DK 8703138	A	19871221	DK 1987-3138	19870619
	NO 8702589	A	19871221	NO 1987-2589	19870619
	JP 63039855	A2	19880220	JP 1987-153219	19870619
	JP 2542620	B2	19961009		
	JP 08283153	A2	19961029	JP 1995-246555	19870619
	US 5061710	A	19911029	US 1987-133669	19871216
	AU 9068517	A1	19910718	AU 1990-68517	19901227
	AU 636423	B2	19930429		
	US 4801609	B1	19931109	US 1991-90002282	19910214
	US 5262436	A	19931116	US 1991-741025	19910806
	JP 08176100	A2	19960709	JP 1995-246554	19950821
PRAI	US 1986-876610		19860620		
	US 1987-32153		19870327		
	EP 1987-108730		19870617		
	JP 1987-153219		19870619		
	US 1987-133669		19871216		

OS MARPAT 109:48448

09986629

AB Neutral metalloendopeptidase (NMEP) inhibitor is used alone or combined with an atrial peptide or an angiotensin converting enzyme (ACE) inhibitor for preparation of pharmaceutical compns. for treating hypertension. The compns. are obtained by mixing a NMEP inhibitor, alone or combined with an atrial peptide or ACE inhibitor, with a pharmaceutically acceptable carrier. S-(4-Methylbenzyl)-L-cysteine, Me ester hydrochloride was prepared by adding thionyl chloride dropwise to N-tert-butyloxycarbonyl-S-(4-methylbenzyl)-L-cysteine in MeOH, heating the mixture under reflux for 90 min, cooling to room temperature, and concentrating in vacuo. Rats with induced hypertension were dosed s.c. with N-(N-[L-1-(2,2-dimethyl-1-oxopropoxy)methoxy]carbonyl)-2-phenylethyl)-L-phenylalanine]-β-alanine and 1-[(2S)-3-mercapto-2-methyl-1-oxypropyl]-L-proline in Me cellulose vehicle to give a 1-, 2-, 3-, and 4-h decrease in blood pressure of 14, 19, 19, and 15 mMHg vs. an increase of 14, 11, 11, and 8 with the NMEP inhibitor alone and a decrease of 11, 7, 1, and 1 mMHg with the ACE inhibitor alone.

L3 ANSWER 129 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:437131 CAPLUS
DN 109:37131
TI Growth promotion by oral administration of enkephalinase inhibitors (thiorphan and acetorphan) in rats and mice
AU Riviere, P. J. M.; Bueno, L.
CS Dep. Pharmacol., Inst. Natl. Rech. Agronom., Toulouse, 31300, Fr.
SO Animal Production (1988), 46(2), 291-5
CODEN: ANIPA8; ISSN: 0003-3561
DT Journal
LA English
AB The effects of long-term oral administration of enkephalinase inhibitors (acetorphan and thiorphan) on food and water intake, live-weight gain, and food conversion efficiency were investigated in growing rats and mice. In rats, daily drenching with acetorphan (an absorbable prodrug of thiorphan) at 1 mg/kg/day for 8 days did not alter food and water consumption but significantly increased live-weight gain (32.0 g for control rats vs. 40.7 g for treated rats) and improved the food conversion efficiency (4.37 g food/g gain for control rats vs. 3.70 g food/g gain for treated rats). In mice, lower doses (0.2 mg/kg/day) of thiorphan and acetorphan given in the drinking water similarly affected live-weight gain (7.7 g vs. 6.0 g in 3-wk-old mice receiving thiorphan and 2.6 g in 5-wk-old mice receiving acetorphan) with a likely improvement in the food conversion efficiency. Thus, oral administration of enkephalinase inhibitors may alter growth in rodents, probably by affecting the digestive process.

L3 ANSWER 130 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:198309 CAPLUS
DN 108:198309
TI Amelioration of naloxone-precipitated opioid withdrawal symptoms by peripheral administration of the enkephalinase inhibitor acetorphan
AU Livingston, S. J.; Sewell, R. D. E.; Rooney, K. F.; Smith, H. J.
CS Welsh Sch. Pharm., UWIST, Cardiff, CF1 3XF, UK
SO Psychopharmacology (Berlin, Germany) (1988), 94(4), 540-4
CODEN: PSCHDL; ISSN: 0033-3158
DT Journal
LA English
AB The effects of 60 min pretreatment with the enkephalinase inhibitor acetorphan were assessed on naloxone-precipitated (2.5 mg/kg i.p.) abstinence in chronically morphinized rats. In addition, the antinociceptive activity of the compound was investigated in mice. I.p. injection (50 mg/kg) in rats attenuated some aspects of the opioid withdrawal syndrome such as burrowing, wet dog shakes, squeal on touch hostility, tachypnoea, ptosis

and rough hair, whereas jumping and escape behavior were increased in acetorphan-treated animals. No effect was observed on withdrawal hypothermia or acute weight loss. Similarly, chronic dosing with acetorphan after withdrawal produced no significant effect on body weight Acetorphan (50 mg/kg i.p.) tailed to produce any antinociceptive activity in the mouse tail immersion test, but potentiated the antinociceptive effect of D-Ala2-D-Leu5-enkephalin. These results are discussed in terms of acetorphan crossing the blood-brain barrier before being hydrolyzed to thiorphan, thus yielding opioid withdrawal relieving effects.

L3 ANSWER 131 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:88299 CAPLUS
DN 108:88299
TI Role of endogenous enkephalins in locomotion evidenced by acetorphan, an "enkephalinase" inhibitor
AU Michael-Titus, Adina; Preterre, Philippe; Giros, Bruno; Costentin, Jean
CS Unite Neuropsychopharmacol. Exp., Cent. Natl. Rech. Sci., St. Etienne du Rouvray, 76800, Fr.
SO Journal of Pharmacology and Experimental Therapeutics (1987), 243(3), 1062-6
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB To investigate whether endogenous enkephalins modulate locomotion the effect of the systemic administration of acetorphan, a parenterally active enkephalinase inhibitor was examined Locomotor activity in mice and rats was considered as an index to the activity of mesolimbic dopoaminergic neurons. Acetorphan injected i.v. induced an increase in locomotion, mice and rats presenting a similar behavioral response. Naloxone, at low doses, blocked the enhanced motor response. The increased locomotion was antagonized by a pretreatment with haloperidol or potentiated by GBR 12783, a potent and specific inhibitor of dopoamine (DA) uptake. The neurotoxic lesion of the mesolimbic DA system with 6-hydroxydopamine abolished the effect of acetorphan. The locomotor hyperactivity induced by the enkephalinase inhibitor probably results from the protection of local endogenous enkephalins and may be mesolimbic DA dependent.

L3 ANSWER 132 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:68796 CAPLUS
DN 108:68796
TI Analgesic effects of metapramine and evidence against the involvement of endogenous enkephalins in the analgesia induced by tricyclic antidepressants
AU Michael-Titus, Adina; Costentin, Jean
CS Unite Neuropsychopharmacol. Exp., UER Med. Pharm., St. Etienne du Rouvray, 76800, Fr.
SO Pain (1987), 31(3), 391-400
CODEN: PAINDB; ISSN: 0304-3959
DT Journal
LA English
AB The analgesic effects of metapramine (META) and clomipramine (CLOM) in the hot plate test and in the test of elec. stimulation of the tail were reversed by naloxone. Acetorphan, an inhibitor of enkephalinase, did not potentiate META- or CLOM-induced analgesia. Furthermore, the 2 tricyclic antidepressants (TCA) did not potentiate intracerebroventricularly injected Met5-enkephalin. Moreover, the administration of the enzymic inhibitor or of Met5-enkephalin led to a slight decrease of the analgesic effect of the TCAs. META clearly reduces nociception and the involvement of endogenous enkephalins in the analgesia induced by TCAs is improbable.

L3 ANSWER 133 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:68755 CAPLUS

09986629

DN 108:68755
TI Enantiomers of thiorphan and acetorphan: correlation between enkephalinase inhibition, protection of endogenous enkephalins and behavioral effects
AU Giros, Bruno; Gros, Claude; Schwartz, Jean Charles; Danvy, Denis; Plaquevent, Jean Christophe; Duhamel, Lucette; Duhamel, Pierre; Vlaiculescu, Adina; Costentin, Jean; et al.
CS Cent. Paul Broca, Inst. Nat. Sante Rech. Med., Paris, 75014, Fr.
SO Journal of Pharmacology and Experimental Therapeutics (1987), 243(2), 666-73
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB In vitro, (R)- and (S)-thiorphan were almost equipotent in inhibiting enkephalinase or thermolysin activities , whereas the (R)-isomer was 44-fold less potent than the (S)-isomer on angiotensin-converting enzyme (ACE) activity. When tested on slices of rat globus pallidus in the presence of bestatin, to block the aminopeptidase pathway of enkephalin degradation, both thiorphan enantiomers ensured a complete protection of endogenous (Met5)enkephalin released by depolarization and a suppression of the increase in the extracellular levels of Tyr-Gly-Gly, a characteristic enkephalin metabolite. These 2 effects occurred at EC50 (half-maximal, effective concentration) values of the 2 enantiomers (10 nM in both cases), consistent with the idea that they were due to enkephalinase inhibition. After i.v. administration of the acetorphan enantiomers to mice, the enkephalinase activity of a rapidly prepared striatal membrane fraction was reduced in a dose-dependent manner with similar ex vivo ED50 values. In contrast, the ACE activity of the same preparation was reduced in a significant manner only by (S)-acetorphan. Striatal levels of endogenous Tyr-Gly-Gly in mice treated with (R)- or (S)-acetorphan in increasing dosages were reduced with ED50 values closely similar to those required for ex vivo enkephalinase inhibition. Similar ED50 values of acetorphan enantiomers also were found in mice for the naloxone-reversible antinociceptive activity of these compds. in the hot-plate jump test, whereas both were inactive in the hot-plate paw licking test. Both compds. also displayed marked antinociceptive activity in the writhing test (1 mg/kg) and enhanced the mouse locomotor activity at similar dosages. Thus, the behavioral and enkephalin-protective activities of thiorphan and acetorphan enantiomers are likely to result from enkephalinase inhibition.

L3 ANSWER 134 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:68695 CAPLUS
DN 108:68695
TI Naloxone-reversible antidiarrheal effects of enkephalinase inhibitors
AU Marcais-Collado, H.; Uchida, G.; Costentin, J.; Schwartz, J. C.; Lecomte, J. M.
CS Unite Neuropsychopharmacol. Exp., UER Med. Pharm., St. Etienne, 76800, Fr.
SO European Journal of Pharmacology (1987), 144(2), 125-32
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Thiorphan and acetorphan, 2 potent inhibitors of enkephalinase, reduced castor oil-induced diarrhea in rats when administered i.v. (or orally, for acetorphan), but not when administered intracerebroventricularly. These effects were more marked during the 90-min period following the castor oil challenge, but were still significant up to 4-8 h after the latter. Acetorphan was .apprx.6 times more potent than thiorphan. The antidiarrheal activity of both compds. was completely prevented in rats receiving naloxone s.c., but not intracerebroventricularly (in the case of thiorphan). In contrast to loperamide, a peripherally acting opiate receptor agonist, the enkephalinase inhibitors did not reduce

gastrointestinal transit as measured in the charcoal meal test. The antidiarrheal activity of enkephalinase inhibitors therefore seems attributable to protection of endogenous opioids, presumably outside the brain, and to reduction of intestinal secretion rather than transit.

L3 ANSWER 135 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:191 CAPLUS
DN 108:191
TI Sulfur-containing acylamino acids. II. Syntheses and angiotensin I converting enzyme-inhibitory activities of N-mercaptoalkanoyl-S-ethyl-L-cysteine
AU Komori, Taketoshi; Asano, Katsumi; Sasaki, Yasuto; Hanai, Hiromi; Morimoto, Shiro; Hori, Mikio
CS Nagoya Res. Lab., Meito Sangyo Co., Ltd., Aichi, 452, Japan
SO Chemical & Pharmaceutical Bulletin (1987), 35(6), 2388-93
CODEN: CPBTAL; ISSN: 0009-2363
DT Journal
LA English
OS CASREACT 108:191
AB N-Mercaptoalkanoyl derivs. of S-containing amino acids were synthesized as candidate angiotensin I-converting enzyme (ACE) inhibitors. Among them, N-[3-mercapto-2-(4-methoxybenzyl)propanoyl]-S-ethyl-L-cysteine was the most potent inhibitor of ACE at 0.045 μM. The maximum hypotensive effect of this compound was almost equal to that of captopril in anesthetized rats.

L3 ANSWER 136 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1987:593872 CAPLUS
DN 107:193872
TI Sulfur-containing acylamino acids. I. Syntheses and angiotensin I converting enzyme-inhibitory activities of sulfur-containing N-mercaptoalkanoyl amino acids
AU Komori, Taketoshi; Asano, Katsumi; Sasaki, Yasuto; Hanai, Hiromi; Seo, Rumi; Takaoka, Masanori; Morimoto, Shiro; Hori, Mikio
CS Nagoya Res. Lab., Meito Sangyo Co., Ltd., Aichi, 452, Japan
SO Chemical & Pharmaceutical Bulletin (1987), 35(6), 2382-7
CODEN: CPBTAL; ISSN: 0009-2363
DT Journal
LA English
OS CASREACT 107:193872
AB N-Mercaptoalkanoyl derivs. of S-containing amino acids were synthesized and examined for inhibitory effects on angiotensin I-converting enzyme (ACE) extracted from rabbit lung. The inhibition of ACE was determined by means of a spectrometric assay with hippuryl-L-histidyl-L-leucine as a substrate. Among the synthesized S-containing compds., N-(2-benzyl-3-mercaptopropanoyl)-S-methyl-L-cysteine (I) and N-(2-benzyl-3-mercaptopropanoyl)-S-ethyl-L-cysteine (II) showed the most potent inhibitory effects on ACE activity. The concns. required for 50% inhibition of ACE were 0.028 and 0.020 μM for I and II, resp.

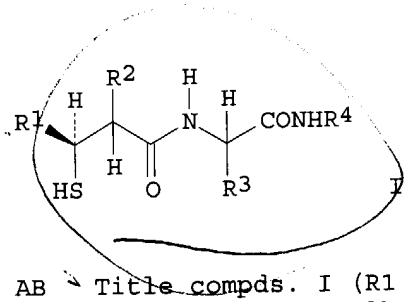
L3 ANSWER 137 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1987:470699 CAPLUS
DN 107:70699
TI Origin of the stimulation of food intake by oral administration of enkephalinase inhibitors in sheep
AU Riviere, P. J. M.; Bueno, L.
CS Dep. Pharmacol., INRA, Toulouse, 31931, Fr.
SO Life Sciences (1987), 41(3), 333-9
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB The effect was studied of 2 enkephalinase inhibitors (thiorphan and acetophan, given orally, parenterally, or centrally) on food intake in

hay-fed ewes. When orally administered at a dose of 1 mg/kg, acetorphan, but not thiorphan, produced a biphasic increase in food intake corresponding to a 17.0% increase of daily food intake. Similarly thiorphan (0.1 mg/kg) i.v. administered increased by 19.3% the daily food intake; in contrast acetorphan i.v. administered produced a early (0-2 h) decrease followed by a late increase in hay consumption without significant change in the daily food intake. When administered centrally (10 μg/kg), thiorphan, but not acetorphan at the same dose, depressed the early (0-2 h) and daily food intake. Pretreatment with naltrexone (0.1 mg/kg i.v.) blocked the increased food intake induced by oral acetorphan or i.v. acetorphan and thiorphan but did not affect the anorectic effects of centrally given thiorphan. Thus, enkephalinase inhibitors like thiorphan and acetorphan increase daily food intake probably by increasing enkephalin levels in peripheral tissues.

L3 ANSWER 138 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1986:609393 CAPLUS
DN 105:209393
TI N-(Mercaptoalkanoyl) amino acid derivatives as collagenase inhibitors
IN Donald, David K.; Hann, Michael M.; Saunders, John; Wadsworth, Harry J.
PA G.D. Searle and Co., USA
SO U.S., 17 pp. Cont.-in-part of U.S. Ser. No. 685,180, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4595700	A	19860617	US 1985-703973	19850221
	EP 185380	A2	19860625	EP 1985-116284	19851219
	EP 185380	A3	19871104		
	EP 185380	B1	19900411		
	R: DE, FR, GB, IT				
	JP 61152650	A2	19860711	JP 1985-286863	19851219
	JP 06062554	B4	19940817		
	CA 1261867	A1	19890926	CA 1985-498182	19851219
	US 4681966	A	19870721	US 1986-847367	19860402
PRAI	US 1984-685180		19841221		
	US 1985-703973		19850221		

OS CASREACT 105:209393
GI



I

AB Title compds. I (R1 = alkyl, Ph, phenylalkyl; R2 and R4 are alkyl; R3 = alkyl, benzyloxyalkyl, alkoxybenzyl, PhCH2OC6H4CH2) were prepared, and showed antiarthritic activity. I (R1 = R4 = Me, R2 = Me2CHCH2, R3 = 4-MeOC6H4CH2) was prepared from Me2CHCH2CHBrCO2Me and a tyrosine derivative in 7 steps. Selected I inhibited human rheumatoid synovial collagenase with IC50 = 0.45-37 μ/M.

L3 ANSWER 139 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1986:491131 CAPLUS
DN 105:91131

09986629

TI Pharmacological properties of acetorphan, a parenterally active "enkephalinase" inhibitor
AU Lecomte, Jeanne Marie; Costentin, Jean; Vlaiculescu, Adina; Chaillet, Pierre; Marcais-Collado, Helene; Llorens-Cortes, Catherine; Leboyer, Marion; Schwartz, Jean Charles
CS Lab. Bioprojet, Paris, Fr.
SO Journal of Pharmacology and Experimental Therapeutics (1986), 237(3), 937-44
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB In purified enkephalinase (EC 3.4.24.11) [82707-54-8] the inhibitory potency of the lipophilic derivative acetorphan **[81110-73-8]** was approx. 1000 fold less than that of Thiorphan [76721-89-6] but became close to the latter (nanomolar) when it was incubated previously with cerebral membranes. After parenteral administration to mice and rats (1-10 mg/kg), extensive inhibition of cerebral enkephalinase was shown by 1) the depressed enzyme activity in brain membranes from treated animals and 2) the long-lasting potentiation of analgesia elicited by (D-Ala2,Met5)enkephalin (given intracerebroventricularly). This suggests that acetorphan easily enters the brain where the active Thiorphan is released. Parenteral acetorphan elicited a series of naloxone-reversible, opioid-like effects, most of which were described previously with intracerebral Thiorphan or other enkephalinase inhibitors. Antinociceptive effects were found in some tests (hot plate jump and phenylbenzoquinone-induced writhing) but not in others (hot plate licking and tail withdrawal). Antidepressant effect was found in the mouse despair test and antidiarrheal effect in the rat castor oil test. Acetorphan also elicited significant increases and decreases in turnover indexes of serotonin [50-67-9] and noradrenaline [51-41-2], resp., in mouse cerebral cortex. In mice chronically treated with acetorphan, the antinociceptive activity of the compound was not modified markedly and no overt withdrawal symptom could be observed after either treatment interruption or administration of naloxone.

L3 ANSWER 140 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1986:472510 CAPLUS
DN 105:72510
TI In vivo enkephalinase inhibition by acetorphan in human plasma and CSF
AU Spillantini, Maria Grazia; Geppetti, Pierangelo; Fanciullacci, Marcello; Michelacci, Sergio; Lecomte, Jeanne Marie; Sicuteri, Federigo
CS Ist. Patol. Med. Farmacol. Clin., Univ. Firenze, Florence, 50134, Italy
SO European Journal of Pharmacology (1986), 125(1), 147-50
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Thiorphan [76721-89-6], the potent inhibitor of enkephalinase, had some analgesic properties in exptl. animals and in man. The possibility that the i.v. infusion of acetorphan **[81110-73-8]**, a prodrug of thiorphan (26 μg/kg/min for 60 min), could inhibit plasma and cerebrospinal fluid (CSF) enkephalinase in man in vivo was investigated. A decrease of approx. 65% in enzyme activity was observed in both plasma and CSF. Acetorphan did not induce any significant variation of plasma angiotensin-converting enzyme [9015-82-1] activity.

L3 ANSWER 141 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1986:182239 CAPLUS
DN 104:182239
TI Proton NMR configurational correlation for retro-inverso dipeptides: application to the determination of the absolute configuration of "enkephalinase" inhibitors. Relationships between stereochemistry and enzyme recognition

09986629

AU Fournie-Zaluski, M. C.; Lucas-Soroca, E.; Devin, J.; Roques, B. P.
CS Dep. Chim. Org., UER Sci. Pharm. Biol., Paris, 75006, Fr.
SO Journal of Medicinal Chemistry (1986), 29(5), 751-7
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
AB Thiorphan, retro-thiorphan, and derivs. were synthesized and tested as enkephalinase (EC 3.4.24.11) inhibitors. Due to a rapid isomerization process, derivs. of retro-thiorphan, which contains a 2-substituted malonyl moiety, cannot be separated by classical methods. However, a separation of the diastereoisomeric mixture of these retro-thiorphan derivs. was achieved by HPLC. The absolute configuration of each isomer was determined by using an NMR configuration correlation. The inhibitory potency of the various inhibitors indicates that, in the thiorphan series, the affinity for enkephalinase is independent of the stereochem. of the 2-(mercaptomethyl)-1-oxo-3-phenylpropyl moiety. In contrast, in the retro-thiorphan series a 100-fold difference in the inhibitory activity of the 2 enantiomers is observed This indicates that there are large differences in the conformational behavior of the 2 series of inhibitors at the active site of the enzyme.

L3 ANSWER 142 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1984:117010 CAPLUS
DN 100:117010
TI Differences in the structural requirements for selective interaction with neutral metalloendopeptidase (enkephalinase) or angiotensin-converting enzyme. Molecular investigation by use of new thiol inhibitors
AU Fournie-Zaluski, Marie Claude; Lucas, Evelyne; Waksman, Gilles; Roques, Bernard P.
CS Dep. Chim. Org., Cent. Natl. Rech. Scient., Paris, Fr.
SO European Journal of Biochemistry (1984), 139(2), 267-74
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB Despite the similarities in their mechanism of action, the structural requirements for selective interaction with angiotensin-converting enzyme (I) or enkephalinase (II) are different. The inhibitory potency of a series of new mercaptoalkanoyl amino acids were determined on pure I from porcine plasma and on neutral metalloendopeptidase purified from rat brain. This latter enzyme, 1st designated as II, appears to be synaptically involved in the degradation of enkephalins. All tested compds., whose design was based on the classical active-site model of metallopeptidases, were reversible and competitive inhibitors of both enzymes. Owing to the remarkable similarity in the general topol. of metallopeptidases, the differences in optimal binding requirements to II and I were interpreted from crystallog. studies on related enzymes, such as thermolysin and carboxypeptidase A. The large size of the S'1 subsite of II allowed efficient binding (Ki $\approx$ 2-30 nM) of aromatic and bulky hydrophobic residues, such as a cyclohexyl ring. In contrast, a Me group in position P'1 favored inhibitory potency against I, whereas a cyclohexyl ring led to a complete loss of activity. This feature could mean that optimal binding of the Zn atom present in the catalytic site is a more stringent requirement in I than in II. An increase in the size of the P'2 component of thiol inhibitors potentiated the affinity for I without a significant change on II. Finally, methylation of the ultimate amide bond of inhibitors produced a 30-fold decrease in potency toward II, but did not affect the binding of I. These findings allowed a rational design of selective inhibitors of II, an essential prerequisite for their possible clin. use as new analgesic and psychoactive agents.

L3 ANSWER 143 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1984:52016 CAPLUS
DN 100:52016
TI Mercaptobenzyl amino acid derivatives
PA Meito Sangyo Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 58140065	A2	19830819	JP 1982-18885	19820210
	JP 03018620	B4	19910313		
PRAI	JP 1982-18885		19820210		

AB Thirty title derivs. RS(CH2)mCH(CH2Ph)CONHCH(CO2H)(CH2)nZR1 I (R = H, alkyl, Bz, carboxyalkyl, carboxyaralkyl; R1 = alkyl; Z = S, SO2; m = 0, 1; n = 1, 2) were prepared by amidation of H2NCH(CO2H)(CH2)nZR1 (II) with R2S(CH2)mCH(CH2Ph)CO2H III (R2 = alkyl, Bz, carboxyalkyl, carboxyaralkyl) optionally followed by treatment with an acid or alkali. I are useful as remedies for angiotensin-related hypertension and liver diseases (no data). Thus, 9.71 g EtSCH2CH(CH2Ph)COCl was added to a mixture of S-Me cysteine and 40 mL N NaOH in Et2O at 5-10° by keeping weakly alkaline with 40 mL N NaOH to give, after stirring overnight at room temperature, L-I (R = Et, R1 = Me, Z = S, m = n = 1).

L3 ANSWER 144 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1984:39596 CAPLUS
DN 100:39596
TI Enkephalinase inhibitors
IN Greenberg, Roland; Cushman, David W.; Vogt, Richard; Weisenborn, Frank L.; Antonaccio, Michael J.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 9 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4401677	A	19830830	US 1981-310192	19811009
	US 4474795	A	19841002	US 1983-499107	19830527
	US 4474799	A	19841002	US 1983-499119	19830527
PRAI	US 1981-310192		19811009		

OS CASREACT 100:39596
AB Enkephalinase [70025-49-9] is inhibited by HSCH2CHR1CONHCHR2CO2H [R1 = C1-4 alkyl, PhCH2, and PhCH2CH2, R2 = C1-4 alkyl, Ph(CH2)n, etc., n = 1-4}, and these inhibitors are used for the alleviation of pain and administered in tablets, capsules, etc. Thus, 3-hydroxy-N-(D-3-mercapto-2-methyl-1-oxopropyl)-L-tyrosine (I) [79617-70-2] was prepared by the acylation of 3,4-dihydroxy-L-phenylalanine [59-92-7] with D-3-acetylthio-2-methylpropanoyl chloride [69570-39-4] in the presence of NaOH at 0° at pH 9.0 and subsequent hydrolysis of the resulting N-(D-3-acetylthio-2-methyl-1-oxopropyl)-3-hydroxy-L-tyrosine [88336-15-6] with concentrate NH4OH. Tablets were prepared each containing 100 mg I.

L3 ANSWER 145 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1983:179923 CAPLUS
DN 98:179923
TI Inhibitors of mammalian collagenase
IN Sundeen, Joseph E.; Dejneka, Tamara
PA E. R. Squibb and Sons, Inc., USA

09986629

SO Eur. Pat. Appl., 47 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 67429	A1	19821222	EP 1982-105125	19820611
	EP 67429	B1	19860416		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	US 4382081	A	19830503	US 1981-273142	19810612
	CA 1248296	A1	19890103	CA 1982-401160	19820416
	JP 57212157	A2	19821227	JP 1982-94660	19820601
	JP 04022907	B4	19920420		
	AT 19251	E	19860515	AT 1982-105125	19820611
	US 4424354	A	19840103	US 1982-424735	19820924
PRAI	US 1981-273142		19810612		
	EP 1982-105125		19820611		

OS CASREACT 98:179923
AB RSCH2CHR1CO-(X)m-NH(CH2)nCHR2R3 [R = H, C2-10 alkanoyl, arylcarbonyl; R1 = C3-8 alkyl, C3-7 cycloalkyl, aryl, aralkyl; R2 = H, carbamoylalkyl, guanidinoalkyl; R3 = CONH2, CN, CHO, CO2R4 (R4 = H, alkyl, aralkyl), CHR5R6 [R5, R6 = OMe, OEt; R5R6 = O(CH2)nO (n = 2, 3)], NR7R8 [R7, R8 = H, alkyl; R7R8 = (CH2)4, (CH2)5, CH2CH2OCH2CH2], Cl, Br, guanidino, OR9 (R9 = H, alkyl, Ac, Bz); X = amino acid residue, di- or tripeptide residue; m = 1, 2, 3; n = 0-7] were prepared as mammalian collagenase inhibitors (no data). Thus, Me2CHCH2CH(CO2H)2 underwent the Mannich reaction with CH2O and Me2NH to give Me2CHCH2C(CO2H)2CH2NMe2, which underwent an elimination reaction in aqueous NaOH to give Me2CHCH2C(:CH2)CO2H, which was treated with AcSH to give Me2CHCH2CH(CH2SAc)CO2H. The latter was condensed with alanine by DCC/N-hydroxysuccinimide to give (±)-Me2CHCH2CH(CH2SAc)CO-L-Ala-OH, which was used in the synthesis of Me2CHCH2CH(CH2SH)CO-L-Ala-Gly-L-Leu-L-Arg-OH by conventional peptide coupling reactions.

L3 ANSWER 146 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1982:598571 CAPLUS
DN 97:198571
TI Compounds for alleviating angiotensin related hypertension
IN Ondetti, Miguel A.; Cushman, David W.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 11 pp. Cont.-in-part of U.S. Ser. No. 773,864, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4339600	A	19820713	US 1978-877197	19780213
	US 4053651	A	19771011	US 1976-684606	19760510
PRAI	US 1976-684606		19760510		
	US 1977-773864		19770303		

OS CASREACT 97:198571
AB RSCHR1CONR2CHR3CO2H (I; R = H, alkanoyl, Bz; R1, R2 = H, alkyl, phenylalkyl; R3 = amino acid side chain) and the disulfides of I (R = H) were prepared as antihypertensives due to their ability to inhibit angiotensin-converting enzyme (ACE). Thus, alanine was acylated with BrCH2CH2COCl in aqueous NaOH for 3.5 h at room temperature and the resulting mixture was treated with thiobenzoic acid to give BzSCH2CH2CO-Ala-OH, which was debenzoylated by aqueous NH4OH to give HSCH2CH2CO-Ala-OH (II). II at 1.2 μg/mL inhibited ACE by 50%.

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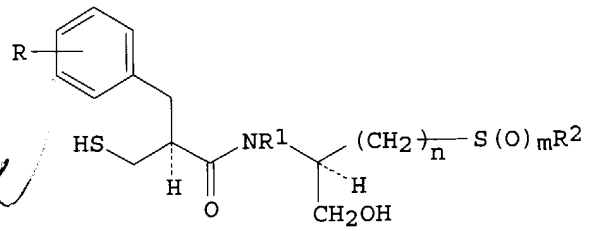
L3 ANSWER 147 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1982:562612 CAPLUS
DN 97:162612
TI Enkephalinase enzyme inhibiting compounds
IN Bindra, Jasjit S.
PA Pfizer Inc., USA
SO U.S., 11 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4329495	A	19820511	US 1981-264752	19810518
	IN 158365	A	19861101	IN 1982-DE263	19820330
	EP 66956	A1	19821215	EP 1982-302387	19820511
	EP 66956	B1	19840808		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	AT 8881	E	19840815	AT 1982-302387	19820511
	NO 8201595	A	19821119	NO 1982-1595	19820513
	NO 153768	B	19860210		
	NO 153768	C	19860521		
	HU 30042	O	19840228	HU 1982-1506	19820513
	HU 188058	B	19860328		
	CA 1179368	A1	19841211	CA 1982-402956	19820514
	PL 138043	B1	19860830	PL 1982-236425	19820514
	DK 8202211	A	19821119	DK 1982-2211	19820517
	DK 160711	B	19910408		
	AU 8283759	A1	19821125	AU 1982-83759	19820517
	AU 529511	B2	19830609		
	JP 57193450	A2	19821127	JP 1982-82977	19820517
	JP 63007542	B4	19880217		
	ZA 8203386	A	19830330	ZA 1982-3386	19820517
	ES 512278	A1	19830601	ES 1982-512278	19820517
	IL 65799	A1	19851231	IL 1982-65799	19820517
	FI 76555	B	19880729	FI 1982-1736	19820517
	FI 76555	C	19881110		
	ES 519668	A1	19840301	ES 1983-519668	19830209
PRAI	US 1981-264752		19810518		
	EP 1982-302387		19820511		

OS CASREACT 97:162612
GI



I

AB I (R = H, C1-3 alkyl or alkoxy, F, Cl, Br, CF3; R1 = H or C1-3 alkyl; R2 = C1-3 alkyl; m = 0, 1, 2; n = 1-4) were prepared as anticonvulsants and analgesics. Thus, BzSCH2CH(CH2Ph)CO2H was converted into the acid chloride, treated with (S)-MeSCH2CH2CH(NH2)CH2OH, and the diastereomers separated and hydrolyzed to give (S)-MeSCH2CH2CH[NHCOCH(CH2Ph)CH2SH-(R) and -(S)]CH2OH.

L3 ANSWER 148 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1982:123304 CAPLUS
DN 96:123304
TI Amino acid derivatives and their therapeutic use
IN Roques, Bernard; Schwartz, Jean Charles; Lecomte, Jeanne Marie
PA Fr.
SO Eur. Pat. Appl., 63 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 38758	A1	19811028	EP 1981-400621	19810417
	EP 38758	B1	19850306		
	R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	FR 2480747	A1	19811023	FR 1980-8601	19800417
	US 4513009	A	19850423	US 1981-254208	19810414
	AT 12042	E	19850315	AT 1981-400621	19810417
	FR 2537131	A1	19840608	FR 1982-20188	19821202
	FR 2537131	B1	19860509		
PRAI	FR 1980-8601		19800417		
	EP 1981-400621		19810417		

OS CASREACT 96:123304
AB RXCH[CH2)nR1]X1X2CHR2COR3 [I; R = H, substituted C1-2 alkyl, acyl, Bz, alkoxycarbonyl, SH, acylthio, BzS, (un)substituted Ph alkylcarbonylthio, hydroxyalkylcarbonylthio, aminoalkylcarbonylthio; X = S, NH, CH2; n = 0, 1; R1 = H, (un)substituted alkyl, cyclohexyl, thienyl; X1 = CO, CH2, NH; X2 = NH, C1-4 alkylimino, CO, S; R2 = H, C1-6 alkyl, Ph, (un)substituted CH2Ph, hydroxyalkyl, (un)substituted alkoxyalkyl, phenoxyalkyl, (un)substituted mercaptoalkyl; R3 = OR4, NHR4, NR42 [R4 = H, (un)substituted C1-8 alkyl, Ph, dialkylaminoalkyl]] were prepared as enkephalinase inhibitors. I can be used as analgesics, potentiators of the analgesic activity of enkephalin, and antihypertensives. Thus, 10 g H-Phe-Leu-OMe.CF3CO2H was treated with 3.34 g EtO2CCH2Br in C6H6 containing Et3N to give 2.6 g EtO2CCH2-Phe-Leu-OMe, which (2.5 g) was saponified by 1N NaOH to give 1.35 g HO2CCH2-Phe-Leu-OH (II). II at 1.5 + 10-6 M inhibited enkephalinase by 50%; II also potentiated the analgesic activity of [D-Ala2]-Met-enkephalin.

L3 ANSWER 149 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1982:123301 CAPLUS
DN 96:123301
TI Pharmaceutical amides, their formulations and their use
IN Wilkinson, Samuel
PA Wellcome Foundation Ltd., UK
SO Eur. Pat. Appl., 50 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 38046	A2	19811021	EP 1981-102770	19810410
	EP 38046	A3	19820120		
	EP 38046	B1	19840229		
	R: BE, CH, DE, FR, GB, LU, NL, SE				
	GB 2074571	A	19811104	GB 1981-11322	19810410
	GB 2074571	B2	19840215		
	JP 56158746	A2	19811207	JP 1981-54256	19810410
PRAI	GB 1980-11986		19800411		

AB RCH2CH(CH2R1)CONHCH(CHR2R3)COR4 [R = ligand for Zn2+; R1 = (un)substituted

Ph; R2 = H, Me; R3 = alkyl, CH2SMe; R4 = OR5 [R5 = H, alkyl, alkylphenyl, Ph], NR6R7 (R6, R7 = H, alkyl)] were prepared as analgesics due to their ability to inhibit enkephalinase. Thus, PhCH2O2CCH2C(:CHPh)CO2H was condensed with H-L-Leu-OCH2Ph.HCl by DCC/1-hydroxybenzotriazole in DMF containing Et3N to give PhCH2O2CCH2C(:CHPh)CO-L-Leu-OCH2Ph, which was hydrogenated over Pd/C to give (RS)-HO2CCH2CH(CH2Ph)CO-L-Leu-OH [(RS)-L-I], which was separated into (R)-L-I and (S)-L-I. The latter at 7.2 + 10-6 and 4.0 + 10-6 M, resp., inhibited enkephalinase by 50%. The antinociceptive activity of (RS)-L-I was measured.

L3 ANSWER 150 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1982:104789 CAPLUS
DN 96:104789
TI Inhibitors of mammalian collagenase
IN Sundeen, Joseph E.; Dejneka, Tamara
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 9 pp. Divison of U.S. 4,235,885.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4297275	A	19811027	US 1980-121352	19800214
PRAI	US 1979-51195		19790625		

OS CASREACT 96:104789
AB RSCH2CH(CH2CHMe2)COR1 [R = H, C2-10 alkanoyl; R1 = OH, NH(CH2)nCHR2COR3 [R2 = H, C1-4 alkyl, (CH2)3NHC(:NH)NH2, CH2CH2CONH2; R3 = OH, NH2, X-OH (X = Arg, Leu, Gln, Ala, Gly); n = 0-9]] were prepared as inhibitors of mammalian collagenase (no data). Thus, Me2CHCH2CH2CO2H was condensed with paraformaldehyde in THF containing BuLi and (Me2CH)2NH at -10 to 10° to give Me2CHCH2CH(CH2OH)CO2H, which was chlorinated with SOCl2 to give Me2CHCH2CH(CH2Cl)COCl, which was treated with glycine to give Me2CHCH2CH(CH2Cl)CO-Gly-OH. The latter underwent dehydrochlorination to give Me2CHCH2C(:CH2)CO-Gly-OH, which was treated with AcSH to give Me2CHCH2CH(CH2SAc)CO-Gly-OH, which was deacetylated by NH4OH to give Me2CHCH2CH(CH2SH)CO-Gly-OH.

L3 ANSWER 151 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1981:157270 CAPLUS
DN 94:157270
TI Mercaptoacyl peptides, their use as ACE inhibitors and in high pressure treatment
IN Ondetti, Miguel A.; Pluscec, Josip
PA E. R. Squibb and Sons, Inc., USA
SO Ger. Offen., 33 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3012140	A1	19801023	DE 1980-3012140	19800328
	AU 8056380	A1	19801009	AU 1980-56380	19800312
	AU 537592	B2	19840705		
	GB 2045771	A	19801105	GB 1980-8696	19800314
	GB 2045771	B2	19830126		
	ZA 8001527	A	19810325	ZA 1980-1527	19800314
	NL 8001675	A	19801006	NL 1980-1675	19800321
	FR 2453135	A1	19801031	FR 1980-6711	19800326
	FR 2453135	B1	19830617		
	NO 8000931	A	19801003	NO 1980-931	19800331

	NO 150360	B	19840625		
	NO 150360	C	19841003		
	SE 8002512	A	19801003	SE 1980-2512	19800401
	DK 8001404	A	19801003	DK 1980-1404	19800401
	ES 490166	A1	19810401	ES 1980-490166	19800401
	HU 181087	B	19830530	HU 1980-774	19800401
	CH 645092	A	19840914	CH 1980-2571	19800401
	BE 882601	A1	19801002	BE 1980-200091	19800402
	JP 55133345	A2	19801017	JP 1980-44020	19800402
	AT 8001794	A	19830615	AT 1980-1794	19800402
	AT 373577	B	19840210		
	US 4684660	A	19870804	US 1980-145516	19800501
PRAI	US 1979-25701		19790402		

AB Title peptides RS(CH2)nCHR1CO-X-X1-OH [R = H, alkanoyl, Bz, S(CH2)nCHR1CO-X-X1-OH; R1 = H, alkyl, phenylalkyl; n = 0, 1; X and X1 = α-amino acid or α-imino acid residue] and their alkyl esters and salts were prepared as antihypertensives (no data) due to their ability to inhibit angiotensin-converting enzyme. Thus, BOC-Val-Pro-OH (BOC = Me3CO2C) was BOC-deblocked and then acylated with AcSCH2CO2NSu (NSu = succinimido) to give AcSCH2CO-Val-Pro-OH, which was deacetylated by aqueous NH3/MeOH to give HSCH2CO-Val-Pro-OH.

L3 ANSWER 152 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1981:103838 CAPLUS
DN 94:103838
TI Inhibitors of mammalian collagenase
IN Dejneka, Tamara; Sundeen, Joseph E.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 9 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4235885	A	19801125	US 1979-51915	19790625
	AU 8058850	A1	19810205	AU 1980-58850	19800528
	AU 539714	B2	19841011		
	ZA 8003198	A	19810527	ZA 1980-3198	19800528
	CA 1180324	A1	19850101	CA 1980-353379	19800604
	EP 21766	A2	19810107	EP 1980-302024	19800616
	EP 21766	A3	19810513		
	EP 21766	B1	19830209		
	R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	JP 56012353	A2	19810206	JP 1980-87211	19800625
	JP 63038024	B4	19880728		
PRAI	US 1979-51915		19790625		

AB R1SCH2CH(CH2CHMe2)COR1 (R2 = H or C2-10 alkanoyl; R2 = OH, NH2, etc.) prepared by several methods can be formulated into pharmaceuticals and used as mammalian collagenase inhibitors. Thus, 2-(mercaptomethyl)-4-methylpentanamide was prepared by conversion of 2-[(acetylthio)methyl]-4-methylpentanoic acid to the acid chloride followed by ammonolysis.

L3 ANSWER 153 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1980:639929 CAPLUS
DN 93:239929
TI Compounds for alleviating hypertension
IN Cushman, David W.; Ondetti, Miguel A.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 13 pp. Cont-in-part of U.S. Ser. No. 876,977 abandoned.
CODEN: USXXAM
DT Patent

09986629

LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4199512	A	19800422	US 1978-943422	19780918
	US 4053651	A	19771011	US 1976-684606	19760510
PRAI	US 1976-684606		19760510		
	US 1977-773864		19770303		
	US 1978-876977		19780213		

AB RS(CHR1)nCHR2CONR3CHR4CO2H [R = H, alkanoyl, Bz, S(CHR1)nCHR2CONR3CHR4CO2H; R1, R2, and R3 = H, alkyl, phenylalkyl; R4 = H, alkyl, R5Z (R5 = indol-3-yl, Ph, OH, HOC6H4, NH2, guanidino, imidazolyl, SH, alkylmercapto, CONH2, CO2H; Z = alkylene); n = 0, 1, 2] were prepared as antihypertensives due to their ability to inhibit angiotensin-converting enzyme (ACE). Thus, alanine was acylated with BrCH2CH2COCl in aqueous NaOH at room temperature for 3.5 h and the resulting mixture was treated with BzSH and K2CO3 in H2O overnight at room temperature to give BzSCH2CH2CO-Ala-OH, which was debenzoylated by aqueous NH4OH to give HSCH2CH2CO-Ala-OH (I). I at 1.2 μg/mL inhibited ACE by 50%.

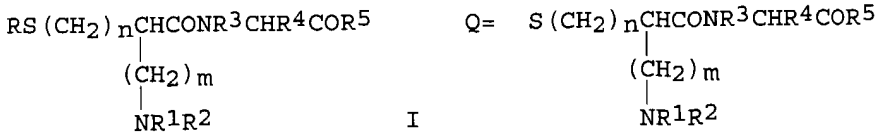
L3 ANSWER 154 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1980:181660 CAPLUS
DN 92:181660
TI Amino acid derivatives
IN Ondetti, Miguel A.; Condon, Michael E.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 10 pp. Cont.-in-part of U.S. 4,113,715.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4179434	A	19791218	US 1978-920602	19780629
	US 4113715	A	19780912	US 1977-759685	19770117
	US 4129571	A	19781212	US 1977-846645	19771031
	US 4284779	A	19810818	US 1977-846734	19771031
	DK 7800169	A	19780718	DK 1978-169	19780113
	DK 149594	B	19860804		
	DK 149594	C	19870316		
	FR 2377374	A1	19780811	FR 1978-1000	19780113
	FR 2377374	B1	19810619		
	GB 1600461	A	19811014	GB 1978-1443	19780113
	CA 1132136	A1	19820921	CA 1978-294939	19780113
	BE 862944	A1	19780516	BE 1978-184354	19780116
	SE 7800503	A	19780717	SE 1978-503	19780116
	SE 445352	B	19860616		
	SE 445352	C	19860925		
	NO 7800151	A	19780718	NO 1978-151	19780116
	NO 150397	B	19840702		
	NO 150397	C	19841010		
	AU 7832440	A1	19800221	AU 1978-32440	19780116
	AU 518282	B2	19810924		
	HU 22919	O	19820728	HU 1978-SU964	19780116
	HU 180529	B	19830328		
	CH 632991	A	19821115	CH 1978-420	19780116
	NL 7800536	A	19780719	NL 1978-536	19780117
	JP 53090218	A2	19780808	JP 1978-4159	19780117
	JP 61026781	B4	19860621		
	US 4284780	A	19810818	US 1978-901372	19780501
	US 4156786	A	19790529	US 1978-919201	19780626

09986629

	US 4154946	A	19790515	US 1978-919880	19780628
	US 4154960	A	19790515	US 1978-920590	19780629
	US 4165320	A	19790821	US 1978-920426	19780629
PRAI	US 1977-759685		19770117		

GI



I

AB Mercaptoalkanoyl amino acids I [R = H, alkanoyl, Bz, Q; R1 = H, alkanoyl, amidino; R2 = H, alkanoyl, phenylalkyl; R3 = H, alkyl, hydroxyalkyl; R4 = H, alkyl, Ph, substituted alkyl; R3R4 = (CH2)p (p = 3, 4); R = OH, alkoxy; n = 0, 1; m = 0-4] were prepared as antihypertensives due to their ability to inhibit angiotensin-converting enzyme. Thus, BOC-D-Cys(CH2C6H4OMe-p)-OH (BOC = Me3CO2C) was coupled to H-Pro-OCMe3 by dicyclohexylcarbodiimide/hydroxybenzotriazole to give BOC-D-Cys(CH2C6H4OMe-p)-Pro-OCMe3, which was deblocked by CF3SO3H/anisole to give H-D-Cys-Pro-OH. H2N(CH2)3CH(CH2SH)CO-X-OH (X = Pro, Arg, Trp) were among several of the other products which were prepared

L3 ANSWER 155 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1979:457527 CAPLUS
DN 91:57527
TI Amino acid derivatives
IN Ondetti, Miguel A.; Condon, Michael E.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 16 pp. Cont.-in-part of U.S. 4,113,715.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4146611	A	19790327	US 1977-846738	19771031
	US 4113715	A	19780912	US 1977-759685	19770117
	US 4129571	A	19781212	US 1977-846645	19771031
	US 4284779	A	19810818	US 1977-846734	19771031
	DK 7800169	A	19780718	DK 1978-169	19780113
	DK 149594	B	19860804		
	DK 149594	C	19870316		
	FR 2377374	A1	19780811	FR 1978-1000	19780113
	FR 2377374	B1	19810619		
	GB 1600461	A	19811014	GB 1978-1443	19780113
	CA 1132136	A1	19820921	CA 1978-294939	19780113
	BE 862944	A1	19780516	BE 1978-184354	19780116
	SE 7800503	A	19780717	SE 1978-503	19780116
	SE 445352	B	19860616		
	SE 445352	C	19860925		
	NO 7800151	A	19780718	NO 1978-151	19780116
	NO 150397	B	19840702		
	NO 150397	C	19841010		
	AU 7832440	A1	19800221	AU 1978-32440	19780116
	AU 518282	B2	19810924		
	HU 22919	O	19820728	HU 1978-SU964	19780116
	HU 180529	B	19830328		
	CH 632991	A	19821115	CH 1978-420	19780116

	NL 7800536	A	19780719	NL 1978-536	19780117
	JP 53090218	A2	19780808	JP 1978-4159	19780117
	JP 61026781	B4	19860621		
	US 4284780	A	19810818	US 1978-901372	19780501
	US 4156786	A	19790529	US 1978-919201	19780626
	US 4154946	A	19790515	US 1978-919880	19780628
	US 4154960	A	19790515	US 1978-920590	19780629
	US 4165320	A	19790821	US 1978-920426	19780629
	US 4177277	A	19791204	US 1978-942563	19780915
PRAI	US 1977-759685		19770117		
	US 1977-846738		19771031		

AB RSCH2CH(NR1R2)CONR3CHR4COR5 [R = H, lower alkanoyl, Bz, SCH2CH(NR1R2)CONR3CHR4COR5; R1 = H, lower alkanoyl, H2NC(:NH); R2 = H, lower alkyl; R3 = H, lower alkyl; R4 = H, lower alkyl, substituted lower alkyl, Ph; R3R4 = (CH2)n (n = 3,4); R5 = H, lower alkoxy], useful as antihypertensives due to their ability to inhibit angiotensin-converting enzyme (ACE), were prepared Thus, BOC-D-Cys(CH2C6H4OMe-p)-OH (BOC = Me3CO2C) was coupled to H-Pro-OCMe3 by dicyclohexylcarbodiimide/hydroxybenzotriazole in CH2Cl2 to give BOC-D-Cys(CH2C6H4OMe-p)-Pro-OCMe3, which was deblocked with CF3SO3H/anisole to give H-D-Cys-Pro-OH (I). I at 0.13 μg/mL inhibited ACE by 50%.

L3 ANSWER 156 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1979:6699 CAPLUS
DN 90:6699
TI Mercaptoacylamino acid derivatives and their salts useful in treating high blood pressure due to angiotensin
IN Ondetti, Miguel A.
PA E. R. Squibb and Sons, Inc., USA
SO Ger. Offen., 25 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2753824	A1	19780608	DE 1977-2753824	19771202
	US 4091024	A	19780523	US 1976-747282	19761203
	CA 1080728	A1	19800701	CA 1977-289603	19771026
	GB 1589933	A	19810520	GB 1977-45787	19771103
	FR 2372804	A1	19780630	FR 1977-35941	19771129
	FR 2372804	B1	19800822		
	JP 53071015	A2	19780624	JP 1977-146519	19771203
	JP 61021226	B4	19860526		
	US 4127729	A	19781128	US 1978-879409	19780221
	US 4128721	A	19781205	US 1978-879410	19780221
	US 4154736	A	19790515	US 1978-879408	19780221
	US 4198517	A	19800415	US 1978-973199	19781226
PRAI	US 1976-747282		19761203		
	US 1978-879408		19780221		

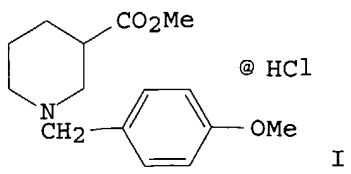
AB RS(CH2)mCH[(CH2)nR1]CONR2CHR3COR4(I) [R = H, Bz, lower alkanoyl, S(CH2)mCH[(CH2)nR1]CONR2CHR3COR4; R1 = CN, lower alkoxycarbonyl, CO2H, CONH2 which may be N-substituted with lower alkyl or Ph lower alkyl; R2 = H, lower alkyl, hydroxy lower alkyl; R3 = H, Ph, lower alkyl which may be substituted by Ph, OH, C6H4OH, NH2, guanidino, imidazolyl, indolyl, SH, lower alkylthio, CONH2, or CO2H; R2R3 = (CH2)p which may be substituted with OH (p = 3, 4); R4 = OH, lower alkoxy; m = 0, 1; n = 0-4] and their basic salts were prepared as antihypertensives due to their ability to inhibit angiotensin-converting enzyme. Thus, MeO2CCH2C(:CH2)CO2H was treated with thioacetic acid to give MeO2CCH2CH(CH2SAc)CO2H which was coupled to H-Pro-OCMe3 by dicyclohexylcarbodiimide/hydroxybenzotriazole to give MeO2CCH2CH(CH2SAc)CO-Pro-OCMe3. The tert-Bu ester was cleaved from

the latter to give the corresponding acid (II) which was saponified to give HO2CCH2CH(CH2SH)CO-Pro-OH. II was hydrolyzed in aqueous NH3 to give MeO2CCH2CH(CH2SH)CO-Pro-OH. I reduced blood pressure with a preferable dosage of 10-500 mg/kg/day.

L3 ANSWER 157 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1978:580372 CAPLUS
DN 89:180372
TI (Acyl-)Mercaptoacylamino acid derivatives useful in combatting angiotensin-caused high blood pressure
IN Ondetti, Miguel A.; Condon, Michael E.
PA E. R. Squibb and Sons, Inc., USA
SO Ger. Offen., 32 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2801911	A1	19780720	DE 1978-2801911	19780117
	DE 2801911	C2	19910321		
	US 4113715	A	19780912	US 1977-759685	19770117
	US 4129571	A	19781212	US 1977-846645	19771031
	US 4284779	A	19810818	US 1977-846734	19771031
	DK 7800169	A	19780718	DK 1978-169	19780113
	DK 149594	B	19860804		
	DK 149594	C	19870316		
	FR 2377374	A1	19780811	FR 1978-1000	19780113
	FR 2377374	B1	19810619		
	GB 1600461	A	19811014	GB 1978-1443	19780113
	CA 1132136	A1	19820921	CA 1978-294939	19780113
	BE 862944	A1	19780516	BE 1978-184354	19780116
	SE 7800503	A	19780717	SE 1978-503	19780116
	SE 445352	B	19860616		
	SE 445352	C	19860925		
	NO 7800151	A	19780718	NO 1978-151	19780116
	NO 150397	B	19840702		
	NO 150397	C	19841010		
	AU 7832440	A1	19800221	AU 1978-32440	19780116
	AU 518282	B2	19810924		
	HU 22919	O	19820728	HU 1978-SU964	19780116
	HU 180529	B	19830328		
	CH 632991	A	19821115	CH 1978-420	19780116
	NL 7800536	A	19780719	NL 1978-536	19780117
	JP 53090218	A2	19780808	JP 1978-4159	19780117
	JP 61026781	B4	19860621		
	US 4284780	A	19810818	US 1978-901372	19780501
	US 4156786	A	19790529	US 1978-919201	19780626
	US 4154946	A	19790515	US 1978-919880	19780628
	US 4154960	A	19790515	US 1978-920590	19780629
	US 4165320	A	19790821	US 1978-920426	19780629
PRAI	US 1977-759685		19770117		

OS CASREACT 89:180372
GI



I

AB Nine R3S(CH2)nCH[(CH2)mNR1R2]CONR4CHR5COR [R = OH, alkoxy; R1 = H, H2NCH2, HN:CH, alkanoyl; R2 = H, alkyl, phenylalkyl; R3 = H, Bz, alkanoyl, S(CH2)nCH[(CH2)mNR1R2]CONR4CHR5COR; R4 = H, alkyl, hydroxyalkyl; R5 = H, Ph, alkyl, Ph-, HO-, HOC6H4-, H2N-, guanidino-, imidazolyl-, indolyl-, HS-, alkylthio-, H2NCO-, HO2C-substituted alkyl; NR4CHR5 = un- or HO-substituted 5- or 6-membered ring; m = 0, 1, 2, 3, 4; n = 0, 1; at least 1 of m or n ≠0] and their salts, useful in decreasing or eliminating high blood pressure caused by angiotensin (no data), were prepared by 5 methods. Thus, Me nipecotate and Cl3CCO2CH2C6H4OMe-4 gave the nipecotate I, which was converted in 9 steps via H2N(CH2)3C(:CH2)CO2H.HCl and 4-MeOC6H4CH2O2CNH(CH2)3CH(CH2SAc)CO-L-Arg-OH to H2N(CH2)3CH(CH2SH)CO-L-Arg-OH.

L3 ANSWER 158 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1978:136977 CAPLUS
DN 88:136977
TI Compounds and method for alleviating angiotensin-related hypertension
IN Ondetti, Miguel Angel; Cushman, David W.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 9 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4053651	A	19771011	US 1976-684606	19760510
	US 4112119	A	19780905	US 1977-773865	19770303
	AU 7724106	A1	19781012	AU 1977-24106	19770407
	AU 513622	B2	19801211		
	ZA 7702256	A	19780329	ZA 1977-2256	19770413
	CA 1119177	A1	19820302	CA 1977-276034	19770413
	GB 1577415	A	19801022	GB 1977-15559	19770414
	DE 2717548	A1	19771201	DE 1977-2717548	19770420
	DE 2717548	C2	19900503		
	CS 204001	P	19810331	CS 1977-2657	19770421
	NL 7704712	A	19771114	NL 1977-4712	19770429
	DD 130477	C	19780405	DD 1977-198728	19770503
	FR 2372624	A1	19780630	FR 1977-13595	19770504
	FR 2372624	B1	19800509		
	PL 106032	P	19791130	PL 1977-205447	19770507
	PL 107991	B1	19800331	PL 1977-197963	19770507
	NO 7701623	A	19771111	NO 1977-1623	19770509
	DK 7702031	A	19771111	DK 1977-2031	19770509
	SE 7705382	A	19771111	SE 1977-5382	19770509
	CH 620202	A	19801114	CH 1977-5766	19770509
	HU 19946	O	19810528	HU 1977-SU947	19770509
	HU 177750	P	19811228		
	BE 854458	A1	19771110	BE 1977-177439	19770510
	JP 52136117	A2	19771114	JP 1977-54201	19770510
	JP 61020544	B4	19860522		
	SU 818479	A3	19810330	SU 1977-2478851	19770510
	FR 2367741	A1	19780512	FR 1978-1417	19780118
	FR 2367741	B1	19821029		
	US 4339600	A	19820713	US 1978-877197	19780213
	CS 204002	P	19810331	CS 1978-1072	19780220
	US 4140786	A	19790220	US 1978-884800	19780309
	US 4140797	A	19790220	US 1978-884943	19780309
	US 4173704	A	19791106	US 1978-918881	19780526
	SU 697049	D	19791105	SU 1978-2632600	19780705
	SU 955857	A3	19820830	SU 1978-2632596	19780705

	US 4199512	A	19800422	US 1978-943422	19780918
	CH 621763	A	19810227	CH 1980-4025	19800522
PRAI	US 1976-684606		19760510		
	US 1977-773864		19770303		
	US 1977-773865		19770303		
	CS 1977-2657		19770421		
	CH 1977-5766		19770509		
	US 1978-876977		19780213		

AB RS(CHRR1)mCHR2CONR3CHR4CO2H [R = H, lower alkanoyl, Bz, S(CHR1)mCHR2CONR3CHR4CO2H; R1, R3, R3 = H, R5Z (R5 = H, Ph, Z = lower alkylene); R4 = H, R6Z1 (R6 = H, Ph, HO, HOC6H4, guanidino, Z1 = lower alkylene); n = O, 1, 2] were claimed as angiotensin-converting enzyme (ACE) inhibitors to be used in the treatment of angiotensin-related hypertension. Thus, alanine was treated with BrCH2CH2COCl and thiobenzoic acid in alkaline H2O to give BzSCH2CH2CO-Ala-OH which was hydrolyzed in aqueous NH4OH to give HSCH2CH2CO-Ala-OH (I). I at 1.2μ g/mL inhibited ACE by 50%.

L3 ANSWER 159 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1978:51171 CAPLUS
DN 88:51171
TI (Acyl) mercaptoacylamino acids useful in treating angiotensin-conditioned high blood pressure
IN Ondetti, Miguel A.; Cushman, David W.
PA E. R. Squibb and Sons, Inc., USA
SO Ger. Offen., 48 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2717548	A1	19771201	DE 1977-2717548	19770420
	DE 2717548	C2	19900503		
	US 4053651	A	19771011	US 1976-684606	19760510
PRAI	US 1976-684606		19760510		

AB Amino acid derivs. R4S(CHR3)nCHR2CONR1CHRCO2H [I; R = H, alkyl, phenylalkyl, or substituted alkyl or phenylalkyl; R1, R2, R3 are independently H, alkyl, phenylalkyl; R4 = H, alkanoyl, Bz, or S(CHR3)nCHR2CONR1CHRCO2H; n = 0, 1, 2], which showed muscle-relaxant and hypotensive activity, were prepared Thus, 4.2 g L-BzS(CH2)2CONHCHMeCO2H was hydrolyzed by treatment for 1 h with 7.5 mL H2O and 6 mL concentrate NH4OH to give 1.87 g L-I (R = Me, R1 = R2 = R3 = R4 = H, n = 1), which had IC50 0.94 μg/mL for lowering Angiotensin I-induced contractions of isolated ileum.